



US009434939B2

(12) **United States Patent**  
**Yu et al.**

(10) **Patent No.:** **US 9,434,939 B2**  
(45) **Date of Patent:** **Sep. 6, 2016**

(54) **INSTRUMENT FOR CASSETTE FOR SAMPLE PREPARATION**

(2013.01); *B01L 3/523* (2013.01); *B01L 3/527* (2013.01); *B01L 2200/10* (2013.01); (Continued)

(71) Applicant: **LUMINEX CORPORATION**, Austin, TX (US)

(58) **Field of Classification Search**

CPC ..... *G01N 2035/00811*; *G01N 2035/0412*; *G01N 2035/0415*; *G01N 2035/00574*; *G01N 35/026*; *C12Q 1/6806*; *B01L 2300/0609*; *B01L 2300/0672*; *Y10S 436/807*; *Y10T 436/11*; *Y10T 436/25*; *B01F 15/0237*  
See application file for complete search history.

(72) Inventors: **Steve Jia Chang Yu**, San Jose, CA (US); **Jesus Ching**, San Jose, CA (US); **Phillip You Fai Lee**, San Francisco, CA (US); **David Hsiang Hu**, Palo Alto, CA (US)

(73) Assignee: **LUMINEX CORPORATION**, Austin, TX (US)

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

2,940,448 A 6/1960 Furlong ..... 600/579  
3,607,094 A 9/1971 Beer ..... 422/63  
(Continued)

(21) Appl. No.: **15/006,494**

**FOREIGN PATENT DOCUMENTS**

(22) Filed: **Jan. 26, 2016**

CA 2626808 4/2007  
DE 10319045 12/2004

(65) **Prior Publication Data**

US 2016/0138010 A1 May 19, 2016

(Continued)

**OTHER PUBLICATIONS**

**Related U.S. Application Data**

Extended Search Report and Opinion, issued in European Application No. 06817150.3, dated May 28, 2014.

(63) Continuation of application No. 14/525,976, filed on Oct. 28, 2014, now Pat. No. 9,273,344, which is a continuation of application No. 13/459,469, filed on Apr. 30, 2012, now Pat. No. 8,900,877, which is a

(Continued)

*Primary Examiner* — Jennifer Wecker

(Continued)

(74) *Attorney, Agent, or Firm* — Parker Highlander PLLC

(51) **Int. Cl.**

*B01J 19/00* (2006.01)  
*G01N 21/62* (2006.01)

(Continued)

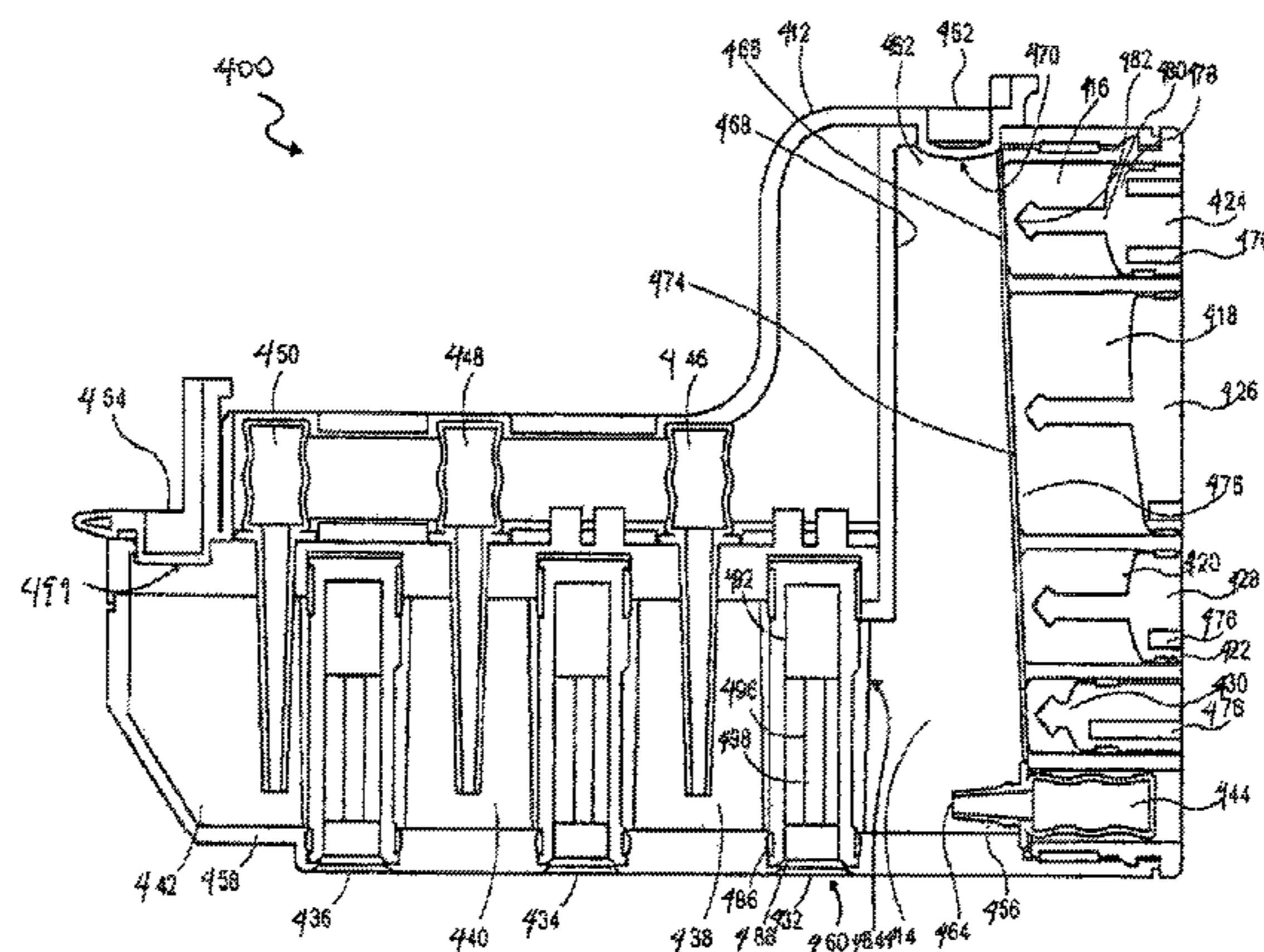
(57) **ABSTRACT**

(52) **U.S. Cl.**

CPC ..... *C12N 15/1013* (2013.01); *G01N 35/0098* (2013.01); *G01N 35/00871* (2013.01); *G01N 35/028* (2013.01); *B01F 15/0237* (2013.01); *B01L 3/502* (2013.01); *B01L 3/502715*

A parallel processing system for processing samples is described. In one embodiment, the parallel processing system includes an instrument interface parallel controller to control a tray motor driving system, a close-loop heater control and detection system, a magnetic particle transfer system, a reagent release system, a reagent pre-mix pumping system and a wash buffer pumping system.

**20 Claims, 14 Drawing Sheets**



**Related U.S. Application Data**

continuation of application No. 13/234,770, filed on Sep. 16, 2011, now Pat. No. 8,168,443, which is a continuation of application No. 13/044,109, filed on Mar. 9, 2011, now Pat. No. 8,029,746, which is a continuation of application No. 12/821,446, filed on Jun. 23, 2010, now Pat. No. 7,910,062, which is a continuation of application No. 12/005,860, filed on Dec. 27, 2007, now Pat. No. 7,754,148.

(60) Provisional application No. 60/882,150, filed on Dec. 27, 2006.

(51) **Int. Cl.**

*C12M 1/00* (2006.01)  
*C12N 15/10* (2006.01)  
*G01N 35/00* (2006.01)  
*G01N 35/02* (2006.01)  
*C12Q 1/00* (2006.01)  
*C12Q 1/68* (2006.01)  
*G01N 35/04* (2006.01)  
*B01F 15/02* (2006.01)  
*B01L 3/00* (2006.01)

(52) **U.S. Cl.**

CPC ..... *B01L2200/16* (2013.01); *B01L 2300/0609* (2013.01); *B01L 2300/0672* (2013.01); *B01L 2400/0478* (2013.01); *C12Q 1/6806* (2013.01); *G01N 35/026* (2013.01); *G01N 2035/00574* (2013.01); *G01N 2035/00811* (2013.01); *G01N 2035/00881* (2013.01); *G01N 2035/0412* (2013.01); *G01N 2035/0415* (2013.01); *Y10S 436/807* (2013.01); *Y10T 436/11* (2015.01); *Y10T 436/25* (2015.01)

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,802,782 A 4/1974 Natelson ..... 356/409  
 4,004,150 A 1/1977 Natelson ..... 250/328  
 4,201,578 A 5/1980 Abbott ..... 430/222  
 4,439,039 A 3/1984 Suovaniemi ..... 356/416  
 4,448,534 A 5/1984 Wertz et al. .... 356/435  
 4,495,149 A 1/1985 Iwata et al. .... 422/65  
 4,626,684 A 12/1986 Landa ..... 250/328  
 4,762,420 A 8/1988 Bowley ..... 356/436  
 5,035,505 A 7/1991 Tsukada et al. .... 356/319  
 5,073,029 A 12/1991 Eberly et al. .... 356/432  
 5,139,745 A 8/1992 Barr et al. .... 422/82.05  
 5,188,455 A 2/1993 Hammerstedt ..... 366/177.1  
 5,229,297 A 7/1993 Schnipelsky et al. .... 436/94  
 5,234,665 A 8/1993 Ohta et al. .... 422/73  
 5,242,660 A 9/1993 Hsei ..... 422/548  
 5,242,837 A 9/1993 Slovacek et al. .... 436/536  
 5,283,624 A 2/1994 Tsukada et al. .... 356/319  
 5,290,513 A 3/1994 Berthold et al. .... 422/52  
 5,307,144 A 4/1994 Hiroshi et al. .... 356/244  
 5,333,675 A 8/1994 Mullis et al. .... 165/268  
 5,348,853 A 9/1994 Wang et al. .... 435/6.12  
 5,389,524 A 2/1995 Larsen et al. .... 435/29  
 5,397,709 A 3/1995 Berndt ..... 436/34  
 5,411,876 A 5/1995 Bloch et al. .... 435/91.2  
 5,415,839 A 5/1995 Zau et al. .... 422/64  
 5,436,718 A 7/1995 Fernandes et al. .... 356/73  
 5,475,610 A 12/1995 Atwood et al. .... 700/269  
 5,494,646 A 2/1996 Seymour ..... 422/401  
 5,500,188 A 3/1996 Hafeman et al. .... 204/403.01  
 5,508,197 A 4/1996 Hansen et al. .... 435/285.1  
 5,511,558 A 4/1996 Shepard et al. .... 600/573  
 5,525,300 A 6/1996 Danssaert et al. .... 422/552  
 5,525,466 A 6/1996 Slovacek et al. .... 435/6.11  
 5,538,849 A 7/1996 Uematsu et al. .... 435/6.19

5,541,072 A 7/1996 Wang et al. .... 435/7.21  
 5,576,197 A 11/1996 Arnold ..... 435/91.2  
 5,578,818 A 11/1996 Kain et al. .... 250/234  
 5,580,523 A 12/1996 Bard ..... 422/50  
 5,585,242 A 12/1996 Bouma et al. .... 435/6.12  
 5,589,136 A 12/1996 Northrup et al. .... 422/129  
 5,616,301 A 4/1997 Moser et al. .... 422/64  
 5,627,041 A 5/1997 Shartle ..... 435/7.24  
 5,639,423 A 6/1997 Northrup et al. .... 422/50  
 5,645,801 A 7/1997 Bouma et al. .... 422/68.1  
 5,656,493 A 8/1997 Mullis et al. .... 435/286.1  
 5,657,118 A 8/1997 Lee ..... 356/246  
 5,661,301 A 8/1997 Weiss ..... 850/26  
 5,665,975 A 9/1997 Kedar ..... 250/573  
 5,674,743 A 10/1997 Ulmer ..... 435/287.2  
 5,686,300 A 11/1997 Berndt ..... 435/287.5  
 5,705,628 A 1/1998 Hawkins ..... 536/25.4  
 5,738,825 A 4/1998 Rudigier et al. .... 422/82.11  
 5,746,978 A 5/1998 Bienhaus et al. .... 422/68.1  
 5,759,784 A 6/1998 Asp et al. .... 435/6.12  
 5,811,312 A 9/1998 Hasegawa et al. .... 436/527  
 5,825,478 A 10/1998 Wilcox et al. .... 356/73  
 5,827,480 A 10/1998 Haff et al. .... 422/68.1  
 5,837,144 A 11/1998 Bienhaus et al. .... 210/695  
 5,861,124 A 1/1999 Hosoi et al. .... 422/82.08  
 5,863,801 A 1/1999 Southgate et al. .... 436/63  
 5,882,903 A 3/1999 Andrevski et al. .... 435/91.2  
 5,897,783 A 4/1999 Howe et al. .... 210/695  
 5,904,899 A 5/1999 Hayashi ..... 422/65  
 5,935,522 A 8/1999 Swerdlow et al. .... 422/70  
 5,989,499 A 11/1999 Catanzariti et al. .... 422/63  
 6,004,512 A 12/1999 Titcomb et al. .... 422/63  
 6,015,674 A 1/2000 Woudenberg et al. .... 435/6.12  
 6,027,945 A 2/2000 Smith et al. .... 436/526  
 6,043,506 A 3/2000 Heffelfinger et al. .... 250/584  
 6,050,719 A 4/2000 Winkler et al. .... 366/144  
 6,057,163 A 5/2000 McMillian ..... 436/172  
 6,061,128 A 5/2000 Zweig et al. .... 356/243.4  
 6,071,748 A 6/2000 Modlin et al. .... 436/174  
 6,096,272 A 8/2000 Clark et al. .... 422/64  
 6,211,989 B1 4/2001 Wulf et al. .... 359/210.1  
 6,222,619 B1 4/2001 Herron et al. .... 356/39  
 6,228,634 B1 5/2001 Blumenfeld et al. .... 435/286.1  
 6,232,608 B1 5/2001 Giebeler et al. .... 250/458.1  
 6,281,008 B1 8/2001 Komai et al. .... 435/306.1  
 6,296,810 B1 10/2001 Ulmer ..... 422/82.07  
 6,297,018 B1 10/2001 French et al. .... 435/5  
 6,353,475 B1 3/2002 Jensen et al. .... 356/244  
 6,358,387 B1 3/2002 Kopf-Sill et al. .... 204/603  
 6,369,893 B1 4/2002 Christel et al. .... 356/417  
 6,429,007 B1 8/2002 Kluttz et al. .... 435/286.5  
 6,431,476 B1 8/2002 Taylor et al. .... 241/1  
 6,440,725 B1 8/2002 Pourahmadi et al. .... 435/288.5  
 6,451,258 B1 9/2002 Malmqvist ..... 422/417  
 6,468,810 B1 10/2002 Korpela ..... 436/526  
 6,492,162 B1 12/2002 Sakurai et al. .... 435/285.1  
 6,517,778 B1 2/2003 Kumar et al. .... 422/82.05  
 6,520,197 B2 2/2003 Deshmukh et al. .... 137/3  
 6,545,758 B1 4/2003 Sandstrom ..... 356/317  
 6,565,815 B1 5/2003 Chang et al. .... 422/198  
 6,569,631 B1 5/2003 Pantoliano et al. .... 506/9  
 6,576,459 B2 6/2003 Miles et al. .... 435/286.5  
 6,597,450 B1 7/2003 Andrews et al. .... 356/317  
 6,645,758 B1 11/2003 Schnipelsky et al. .... 435/287.2  
 6,657,169 B2 12/2003 Brown ..... 219/476  
 6,672,458 B2 1/2004 Hansen et al. .... 209/224  
 6,699,713 B2 3/2004 Bennett et al. .... 435/287.2  
 6,730,501 B2 5/2004 Eyre et al. .... 435/91.2  
 6,730,883 B2 5/2004 Brown et al. .... 219/428  
 6,739,531 B2 5/2004 Taylor ..... 241/1  
 6,764,859 B1 7/2004 Kreuwel et al. .... 436/178  
 6,783,934 B1 8/2004 McMillan et al. .... 435/6.11  
 6,787,338 B2 9/2004 Wittwer et al. .... 435/91.2  
 6,814,934 B1 11/2004 Higuchi ..... 422/82.08  
 6,818,185 B1 11/2004 Petersen et al. .... 422/547  
 6,838,680 B2 1/2005 Maher et al. .... 250/458.1  
 6,852,284 B1 2/2005 Holl et al. .... 422/68.1  
 6,875,602 B2 4/2005 Gutierrez ..... 435/286.2  
 6,890,742 B2 5/2005 Ammann et al. .... 435/91.2

(56)

## References Cited

## U.S. PATENT DOCUMENTS

6,893,879 B2 5/2005 Petersen et al. .... 436/178  
6,908,759 B2 6/2005 Jang ..... 435/285.1  
6,927,852 B2 8/2005 Reel ..... 356/317  
6,955,589 B2 10/2005 Kordonski et al. .... 451/60  
6,982,431 B2 1/2006 Modlin et al. .... 250/573  
6,986,848 B2 1/2006 Ikeda et al. .... 210/695  
7,008,789 B2 3/2006 Gambini et al. .... 435/287.2  
7,027,683 B2 4/2006 O'Connor et al. .... 385/19  
7,078,224 B1 7/2006 Bitner et al. .... 435/270  
7,108,472 B2 9/2006 Norris et al. .... 414/222.07  
7,148,043 B2 12/2006 Kordunsky et al. .... 435/91.2  
7,171,863 B2 2/2007 Tamura et al. .... 73/864.14  
7,223,949 B2 5/2007 Deka et al. .... 219/548  
7,236,237 B2 6/2007 Schmilovitch et al. .... 356/73  
7,284,900 B2 10/2007 Mayer ..... 366/197  
7,294,466 B2 11/2007 McMillan ..... 435/6.12  
7,301,628 B2 11/2007 Cunningham et al. .... 356/326  
7,329,488 B2 2/2008 Roh et al. .... 435/6.19  
7,341,691 B2 3/2008 Tamura et al. .... 422/64  
7,344,894 B2 3/2008 Greenstein et al. .... 436/518  
7,358,078 B2 4/2008 Chen et al. .... 435/286.5  
7,373,253 B2 5/2008 Eyre ..... 702/19  
7,387,891 B2 6/2008 Boege et al. .... 435/288.7  
7,394,547 B2 7/2008 Tan et al. .... 356/480  
7,423,750 B2 9/2008 Hoshizaki et al. .... 356/317  
7,459,302 B2 12/2008 Reid et al. .... 435/286.1  
7,498,164 B2 3/2009 Oldham et al. .... 435/288.7  
7,507,575 B2 3/2009 Bedingham et al. .... 435/287.2  
7,521,179 B2 4/2009 Bachi ..... 435/6.11  
7,584,019 B2 9/2009 Feingold et al. .... 700/245  
7,585,663 B2 9/2009 Shigeura et al. .... 435/287.2  
7,682,565 B2 3/2010 Linton et al. .... 422/68.1  
7,699,979 B2 4/2010 Li et al. .... 210/138  
7,718,072 B2 5/2010 Safar et al. .... 210/695  
7,718,421 B2 5/2010 Chen et al. .... 435/288.5  
7,727,473 B2 6/2010 Ching et al. .... 422/68.1  
7,754,148 B2 7/2010 Yu et al. .... 422/65  
7,910,062 B2 3/2011 Yu et al. .... 422/65  
8,048,386 B2 11/2011 Dority et al. .... 422/500  
8,124,024 B2 2/2012 Ching et al. .... 422/417  
8,133,703 B2 3/2012 Ching et al. .... 435/91.2  
8,168,443 B2 5/2012 Yu et al. .... 436/174  
8,372,340 B2 2/2013 Bird et al. .... 422/63  
2001/0036672 A1 11/2001 Anderson et al. .... 436/180  
2003/0016352 A1 1/2003 Goldman et al. .... 356/317  
2003/0073110 A1 4/2003 Aritomi et al. .... 435/6.12  
2003/0129739 A1 7/2003 Jones ..... 435/287.2  
2003/0170686 A1 9/2003 Hoet et al. .... 435/6.12  
2003/0203491 A1 10/2003 Andreovski et al. .... 436/46  
2003/0224436 A1 12/2003 Nelson et al. .... 435/6.12  
2004/0126783 A1\* 7/2004 Bortolin ..... B01L 3/502  
435/6.12  
2004/0161788 A1 8/2004 Chen et al. .... 435/6.11  
2004/0200909 A1\* 10/2004 McMillan ..... B01L 3/502  
241/1  
2004/0209266 A1 10/2004 Squirrell ..... 435/6.11  
2004/0222395 A1\* 11/2004 Yee ..... F15C 5/00  
251/65  
2004/0259237 A1 12/2004 Kellogg et al. .... 435/287.1  
2005/0194316 A1 9/2005 Pourahmadi et al. .... 210/638  
2005/0244837 A1 11/2005 McMillan et al. .... 435/6.12  
2006/0011539 A1 1/2006 Lee et al. .... 210/613  
2006/0013725 A1 1/2006 Larsen ..... 422/400  
2006/0019379 A1 1/2006 Taylor et al. .... 435/306.1  
2006/0030038 A1 2/2006 Taylor et al. .... 435/306.1  
2006/0165558 A1 7/2006 Witty et al. .... 422/400  
2006/0194264 A1 8/2006 Sheppard et al. .... 435/7.9  
2006/0205085 A1 9/2006 Handique et al. .... 436/177  
2006/0222569 A1 10/2006 Barten et al. .... 422/400  
2006/0246490 A1 11/2006 Anderson et al. .... 435/6.11  
2006/0257991 A1 11/2006 McDevitt et al. .... 435/287.2  
2006/0269922 A1 11/2006 Sagner et al. .... 435/6.18  
2006/0276972 A1 12/2006 Light et al. .... 702/19  
2006/0292032 A1 12/2006 Hataoka et al. .... 422/552  
2007/0036026 A1 2/2007 Laibinis et al. .... 366/273

2007/0054293 A1 3/2007 Liu et al. .... 435/287.2  
2007/0054349 A1 3/2007 Hickey ..... 435/32  
2007/0077646 A1 4/2007 Okamoto ..... 435/288.4  
2007/0087431 A1 4/2007 Ching et al. .... 435/287.2  
2007/0099289 A1 5/2007 Irimia et al. .... 435/287.2  
2007/0125942 A1 6/2007 Kido ..... 250/284  
2007/0212698 A1 9/2007 Bendele et al. .... 435/6.16  
2007/0248958 A1 10/2007 Jovanovich et al. .... 435/6.19  
2007/0281288 A1 12/2007 Belkin et al. .... 435/4  
2007/0292858 A1 12/2007 Chen et al. .... 435/6.18  
2008/0003649 A1 1/2008 Maltezos et al. .... 435/91.2  
2008/0050781 A1 2/2008 Oldham et al. .... 435/91.2  
2008/0153096 A1 6/2008 Witty et al. .... 435/6.12  
2008/0159915 A1 7/2008 Yu et al. .... 422/68.1  
2008/0262213 A1 10/2008 Wu et al. .... 536/25.4  
2008/0280285 A1 11/2008 Chen et al. .... 435/5  
2008/0316482 A1 12/2008 Hoshizaki et al. .... 356/317  
2009/0023201 A1 1/2009 Hongo et al. .... 435/287.2  
2009/0030038 A1 1/2009 Chu et al. .... 514/312  
2009/0130766 A1 5/2009 Weekamp ..... 436/63  
2009/0142745 A1 6/2009 Breidenthal et al. .... 435/3  
2009/0155838 A1 6/2009 Hale ..... 435/29  
2009/0186344 A1 7/2009 Farinas ..... 435/6.11  
2009/0186357 A1 7/2009 Mauk et al. .... 435/6.15  
2009/0215124 A1 8/2009 Cao et al. .... 435/91.2  
2009/0269841 A1 10/2009 Wojciechowski et al. ... 435/325  
2009/0291507 A1 11/2009 Clemmens et al. .... 436/501  
2010/0112567 A1 5/2010 Adolfsen et al. .... 435/6.16  
2010/0239471 A1 9/2010 Ching et al. .... 422/186.01  
2010/0303687 A1 12/2010 Blaga et al. .... 422/504  
2011/0008907 A1 1/2011 Patno et al. .... 436/174  
2011/0158849 A1 6/2011 Yu et al. .... 422/63  
2011/0236960 A1 9/2011 Bird et al. .... 435/283.1  
2012/0003631 A1 1/2012 Yu et al. .... 435/6.1

## FOREIGN PATENT DOCUMENTS

JP 11-271227 5/1999  
JP 2001-108684 4/2001  
JP 2009-512447 3/2009  
JP 2010-505108 2/2010  
WO WO 01/13096 2/2001  
WO WO 2004/005553 1/2004  
WO WO 2004/080597 9/2004  
WO WO 2006/071770 7/2006  
WO WO 2008/037995 4/2008  
WO WO 2009/105711 8/2009  
WO WO 2010/132834 11/2010

## OTHER PUBLICATIONS

Extended Search Report and Opinion, issued in European Application No. 11747970.9, dated May 28, 2014.  
Extended Search Report and Opinion, issued in European Application No. 12779471.7, dated May 28, 2014.  
International Search Report and Written Opinion issued in PCT Application No. PCT/US2006/40835, mailed Dec. 4, 2007.  
International Search Report and Written Opinion issued in PCT Application No. PCT/US2011/25871, mailed May 5, 2011.  
International Search Report and Written Opinion issued in PCT Application No. PCT/US2012/36491, mailed Oct. 5, 2012.  
Office Action, issued in Australian Application No. 2006304623, dated Apr. 21, 2011.  
Office Action, issued in Australian Application No. 2006304623, dated Sep. 9, 2013.  
Office Action, issued in Australian Application No. 2014201790, dated Apr. 23, 2015.  
Office Action, issued in Canadian Application No. 2,626,808, dated Apr. 12, 2013.  
Office Action issued in Canadian Application No. 2,626,808, dated Jan. 10, 2014.  
Office Action, issued in Canadian Application No. 2,626.808, dated Sep. 11, 2014.  
Office Action, issued in Chinese Application No. 200680043554.3, dated Mar. 30, 2011 (English Translation).  
Office Action, issued in Chinese Application No. 201310061818.X, dated Jun. 16, 2014 (English Translation).

(56)

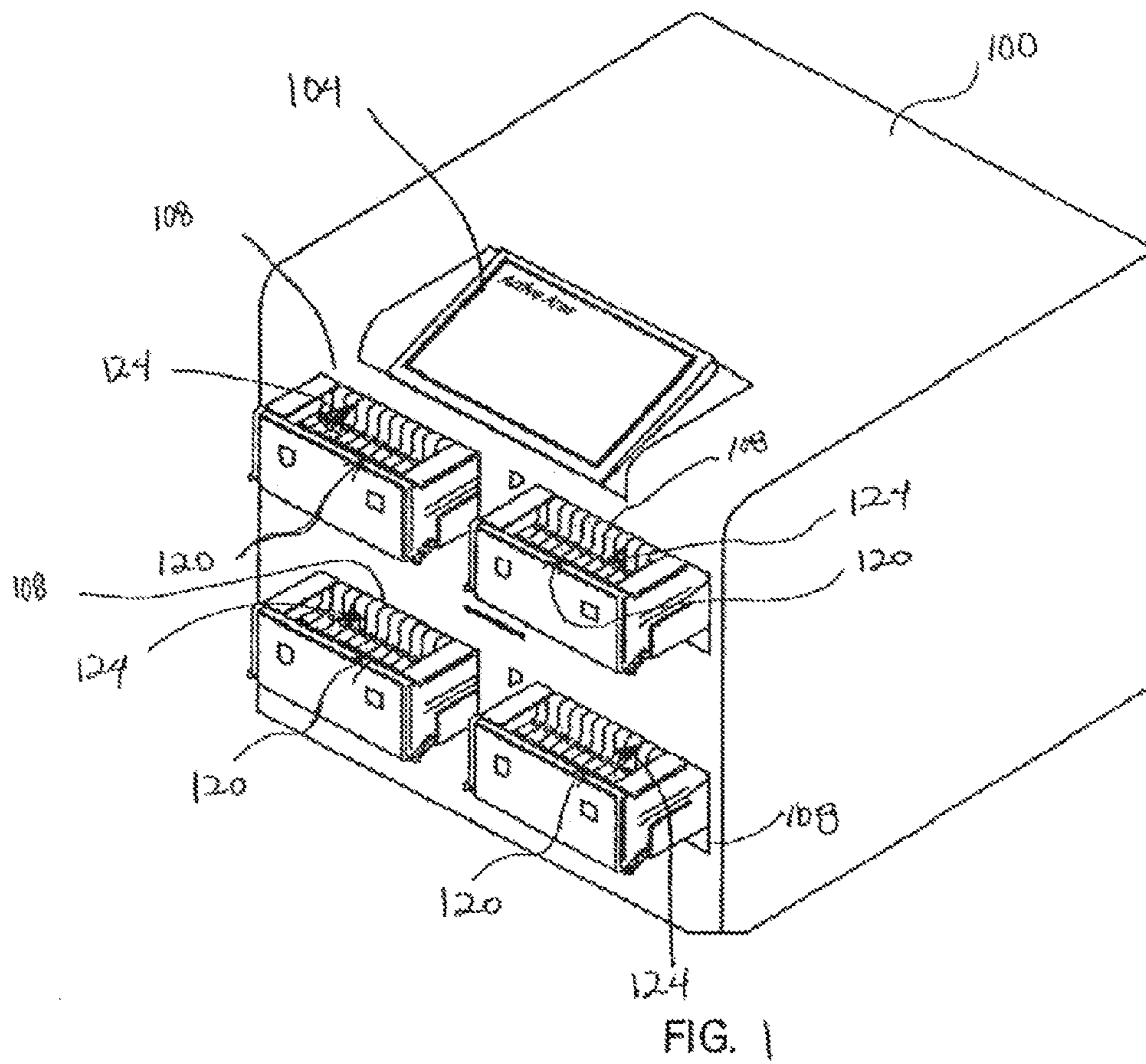
**References Cited**

## OTHER PUBLICATIONS

Office Action, issued in Chinese Application No. 201310061818.X, dated May 11, 2015 (English Translation).  
Office Action, issued in Chinese Application No. 2(11310061818.X, dated Nov. 23, 2015 (English Translation).  
Office Action, issued in European Application No. 06817150.3, dated Mar. 20, 2015.  
Office Action, issued in European Application No. 06817150.3, dated Nov. 13, 2015.  
Office Action issued in Japanese Patent Application No. 2008-536791, mailed Oct. 3, 2011.  
Office Action, issued in Japanese Application No. 2008-536791, dated Jul. 17, 2012 (English Translation).  
Office Action, issued in Korean Application No. 10-2008-7011947, dated May 22, 2013 (English Translation).  
Office Action, issued in Korean Application No. 10-2013-7019433, dated Oct. 21, 2013 (English Translation).  
Office Action, issued in Mexican Application No. MX/a/2008/00511, dated Sep. 7, 2010 (English Translation).  
Office Action, issued in U.S. Appl. No. 12/789,831, dated Nov. 23, 2010.  
Office Action, issued in U.S. Appl. No. 12/789,831, dated May 27, 2011.  
Office Action. issued, in U.S. Appl. No. 13/357,947, dated Oct. 5, 2012.  
Office Action, issued in U.S. Appl. No. 13/910,953, dated Dec. 5, 2013.  
Office Action, issued in U.S. Appl. No. 13/910,953, dated Mar. 28, 2014.  
Office Action, issued in U.S. Appl. No. 12/005,860, dated Nov. 3, 2009.  
Office Action, issued in U.S. Appl. No. 12/821,446, dated Sep. 1, 2010.  
Office Action, issued in U.S. Appl. No. 13/459,469, dated May 15, 2013.  
Office Action, issued in U.S. Appl. No. 13/459,469, dated Oct. 25, 2013.

Office Action, issued in U.S. Appl. No. 13/459,469, dated Mar. 28, 2014.  
Office Action, issued in Australian Application No. 2011220873, dated Aug. 12, 2013.  
Office Action, issued in Australian Application No. 2014224115, dated May 5, 2015.  
Office Action, issued in Canadian Application No. 2,796,586, dated Mar. 31, 2015.  
Office Action, issued in Chinese Application No. 201180018623.6, dated Dec. 26, 2013.  
Office Action, issued in Chinese Application No. 21180018623.6, dated Jul. 15, 2014.  
Office Action, issued in European Application No. 11 747 970.9, dated Apr. 29, 2015.  
Office Action, issued in European Application No. 11 747 970.9, dated Dec. 4, 2015.  
Office Action, issued in Japanese Application No. 2012-555102, dated Feb. 24, 2015.  
Office Action, issued in Japanese Application No. 2012-555102, dated Nov. 10, 2015 (English Translation).  
Office Action, issued in Korean Application No. 10-2012-7024721, date May 19, 2015 (partial English translation).  
Office Action, issued in Korean Application No. 10-2012-7024721, dated Nov. 23, 2015 (partial English translation).  
Office Action, issued in U.S. Appl. No. 13/759,557, dated May 29, 2014.  
Office Action, issued in U.S. Appl. No. 13/759,557, dated Sep. 3, 2014.  
Office Action, issued in Chinese Application No. 201280033332.9, dated Jun. 30, 2015 (English Translation).  
Office Action, issued in European Application No. 12 779 471.7, dated Apr. 9, 2015.  
Office Action, issued in U.S. Appl. No. 13/464,240, dated Nov. 20, 2014.  
Office Action, issued in U.S. Appl. No. 13/464,240, dated Jun. 17, 2015.  
Pilosoof and Nieman, "Microporous membrane flow cell with nonitnmobilized enzyme for chemiluminescent determination of glucose," *Anal. Chem.*, 54:1698-1701, 1982.

\* cited by examiner



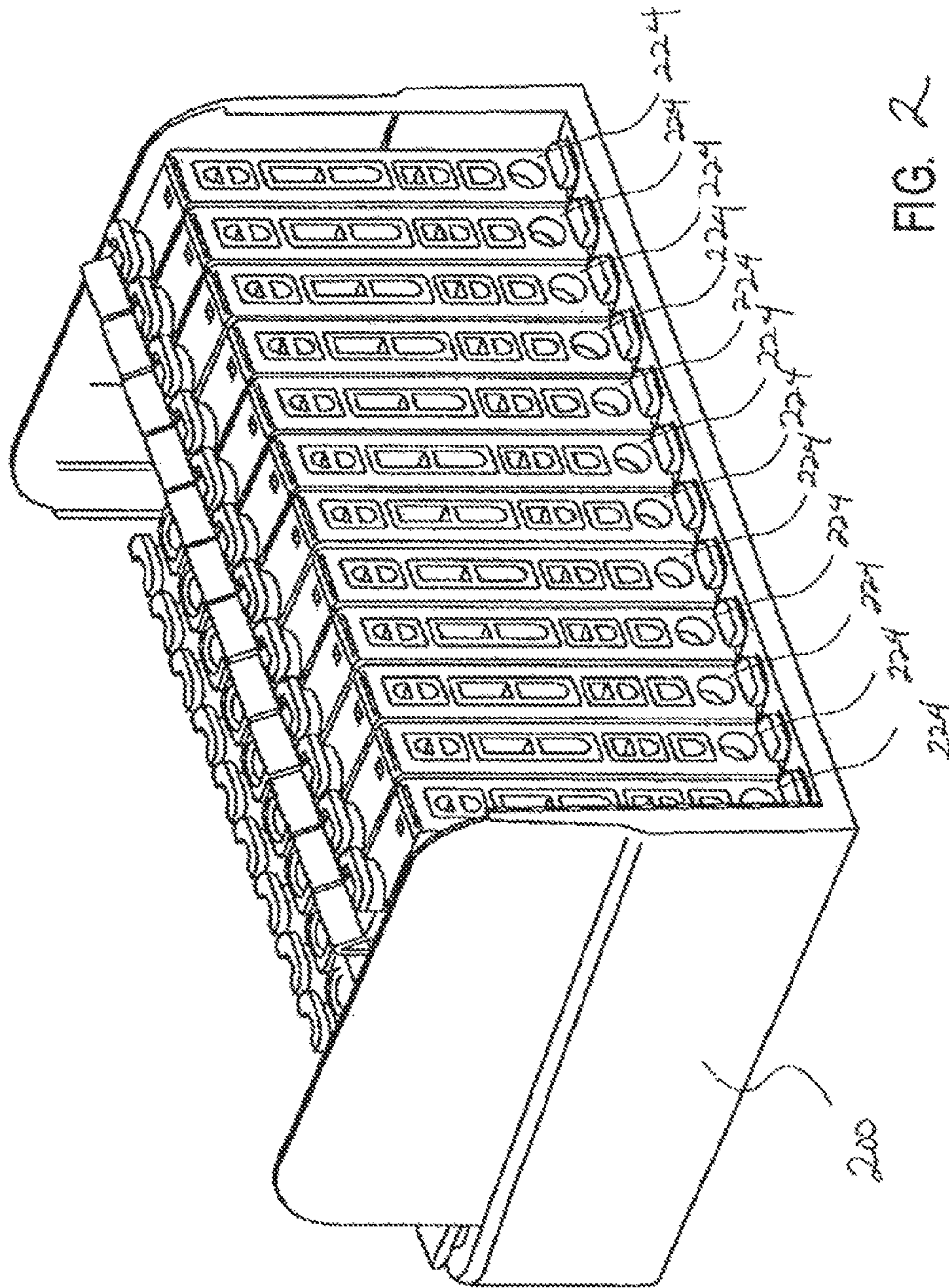


FIG. 2

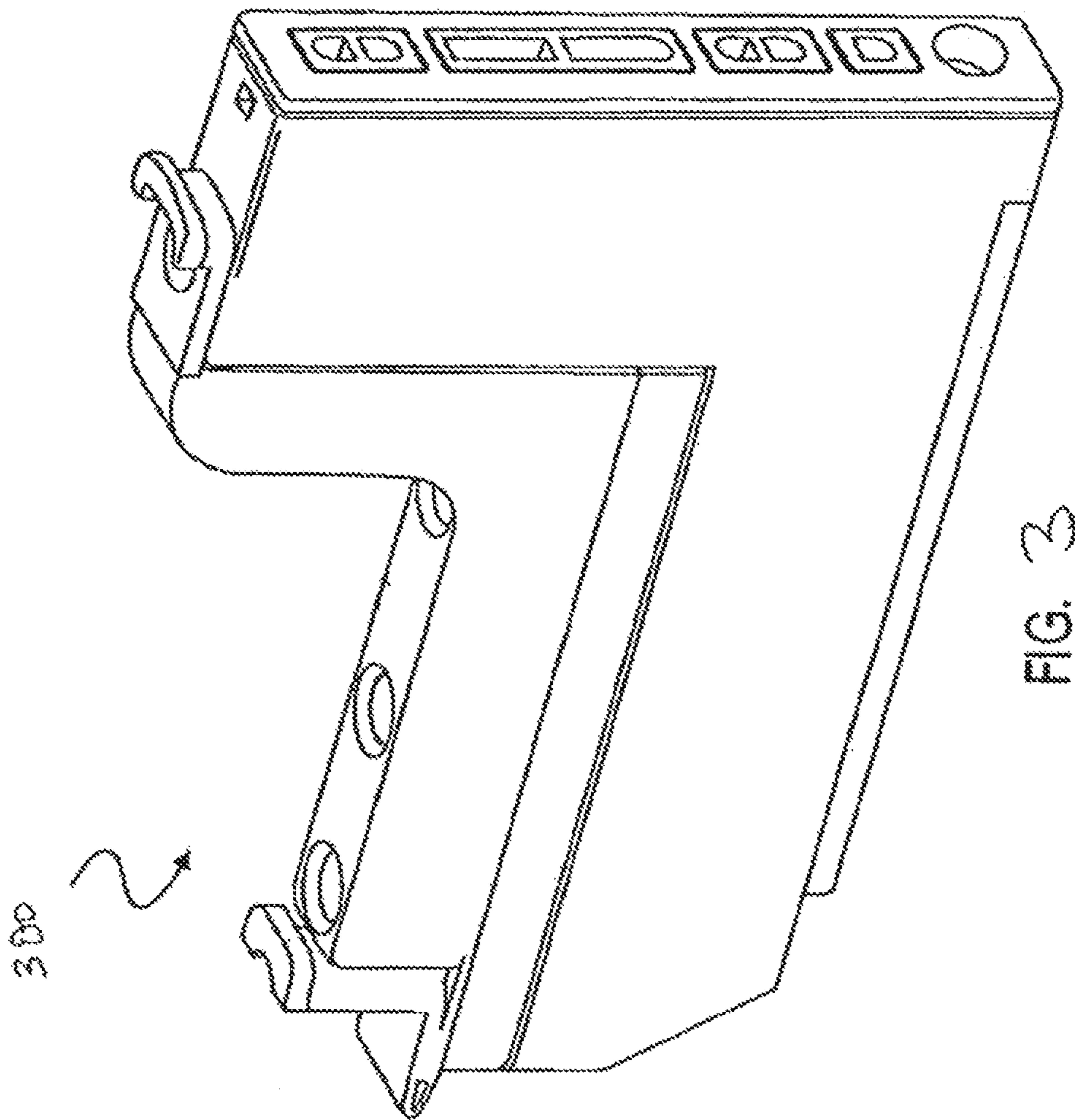


FIG. 3

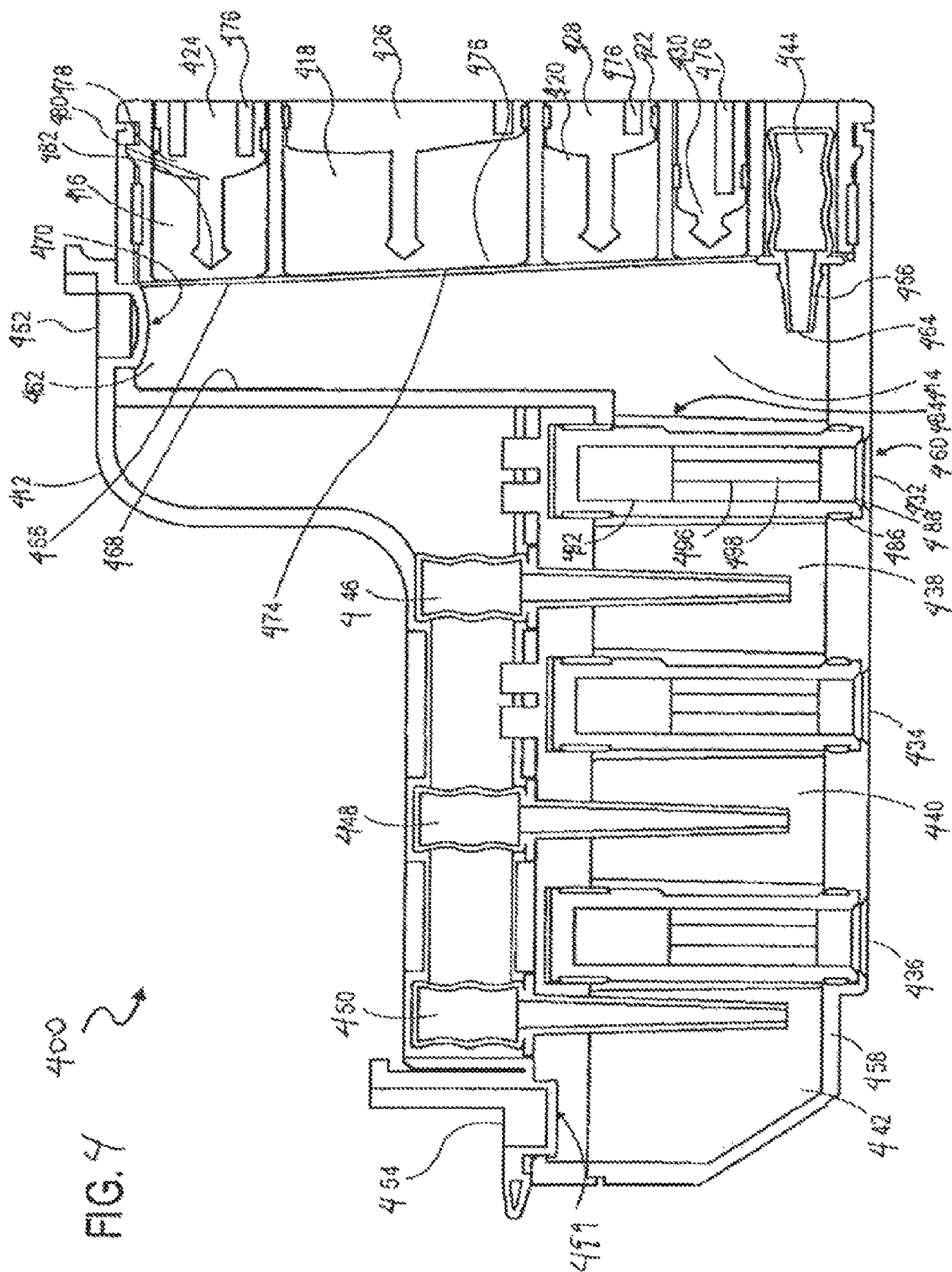


FIG. 4  
400



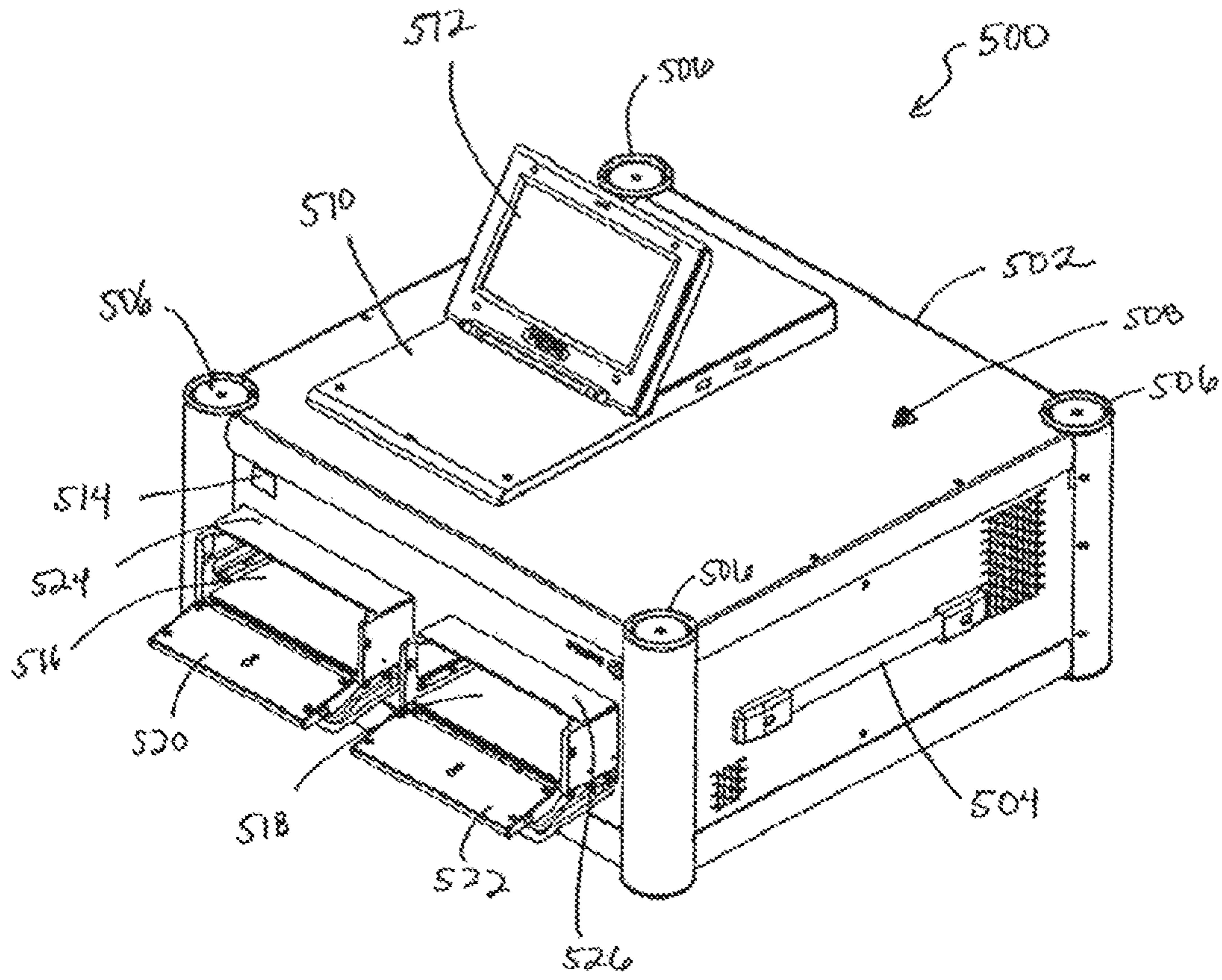


FIG. 5

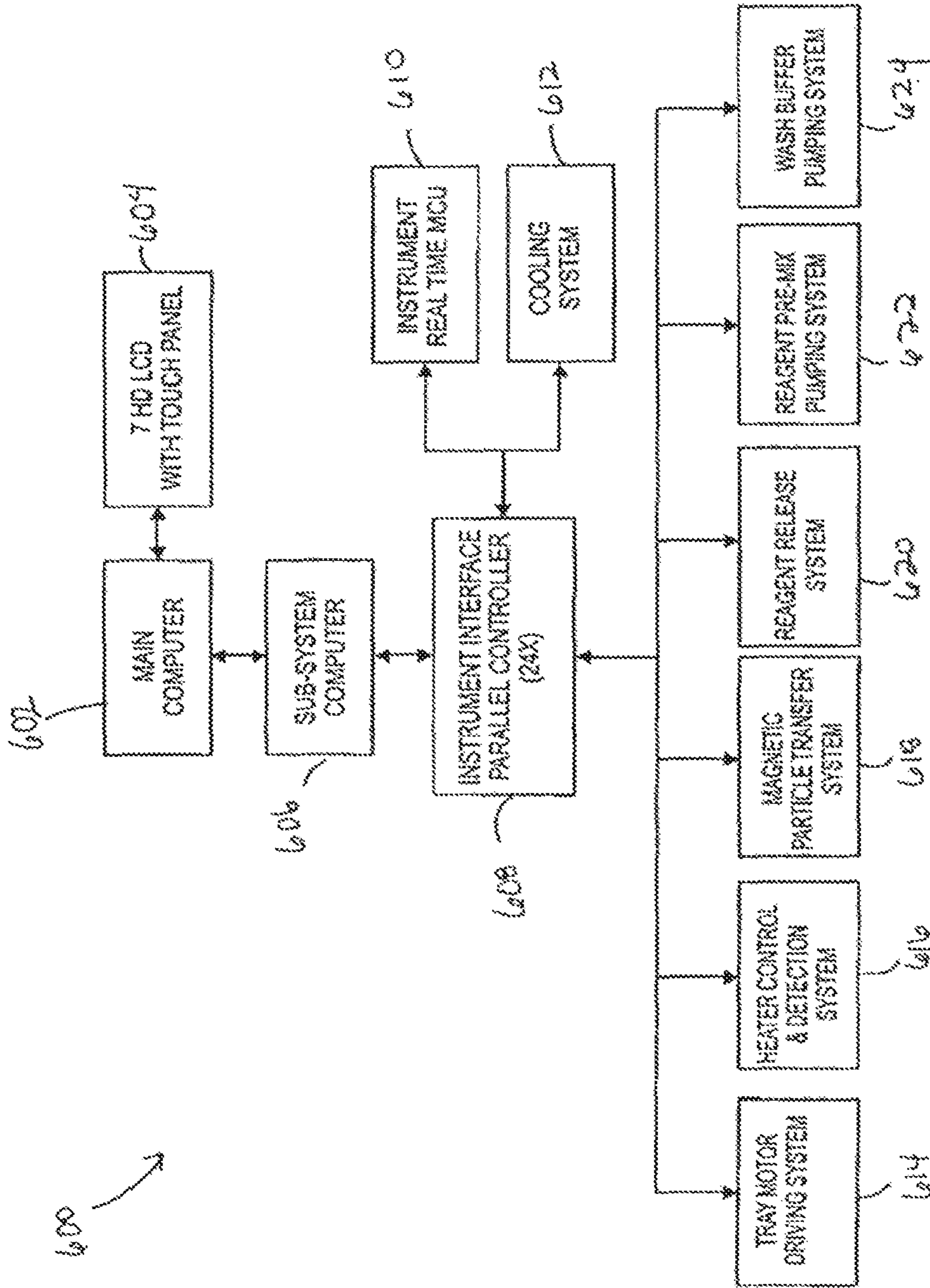


FIG. 6A

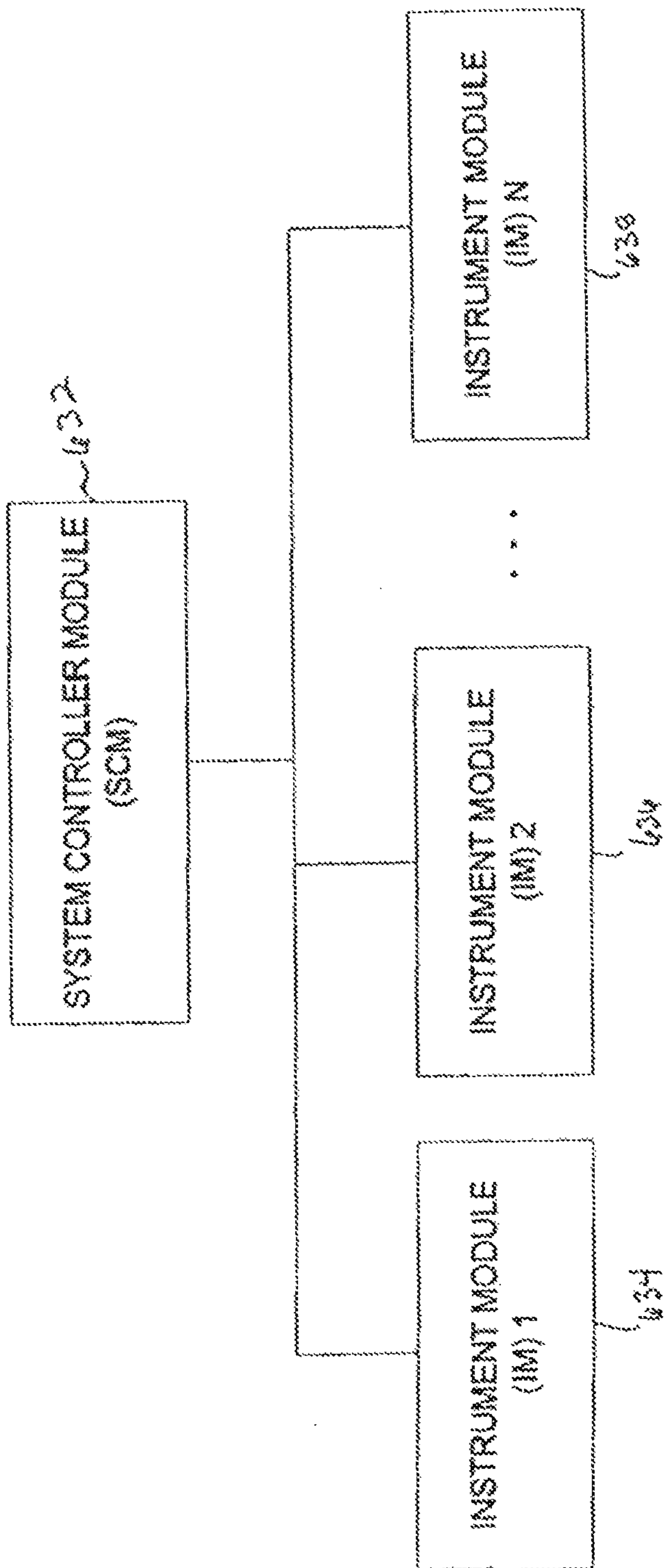


FIG. 6B

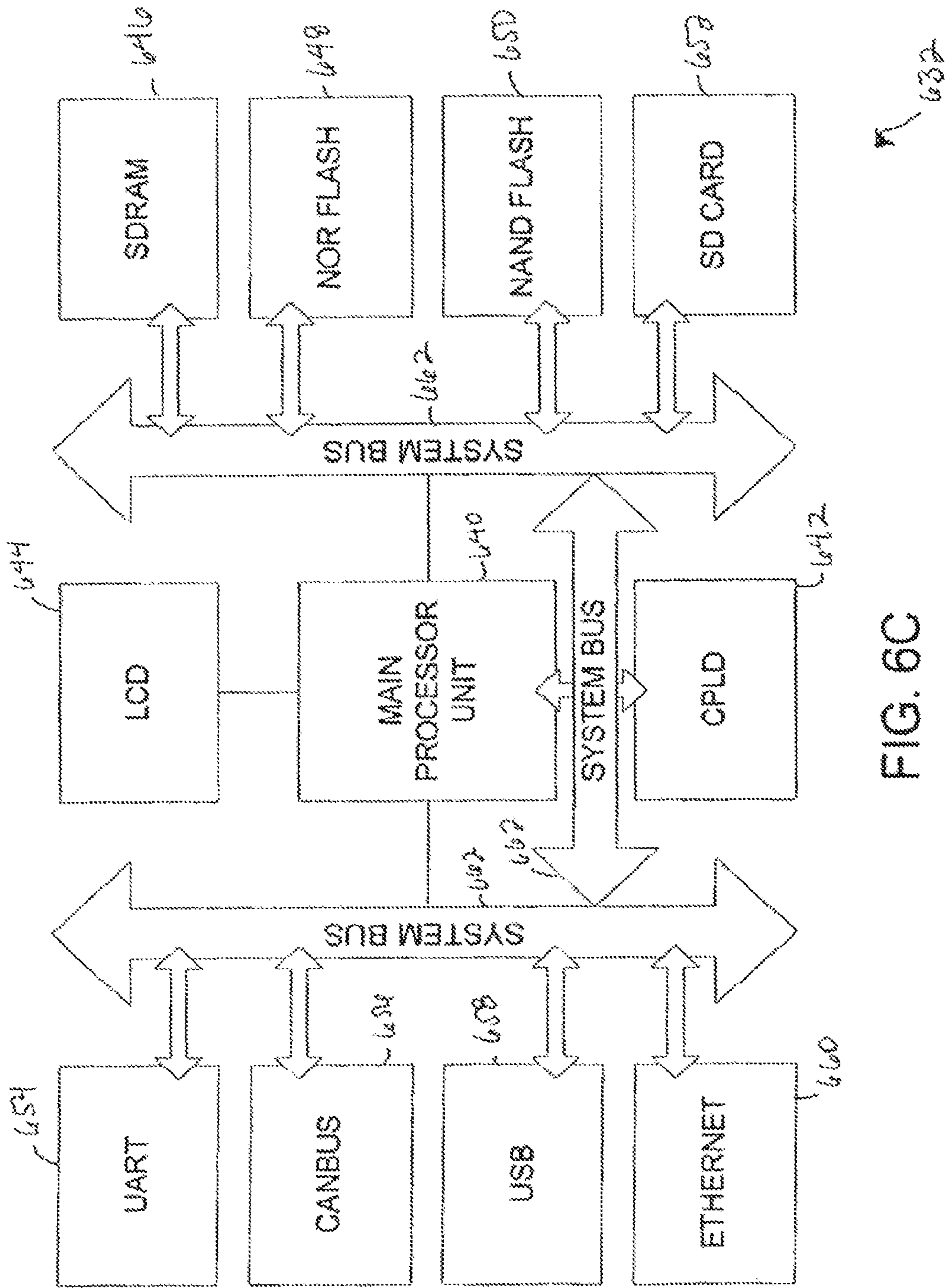


FIG. 6C

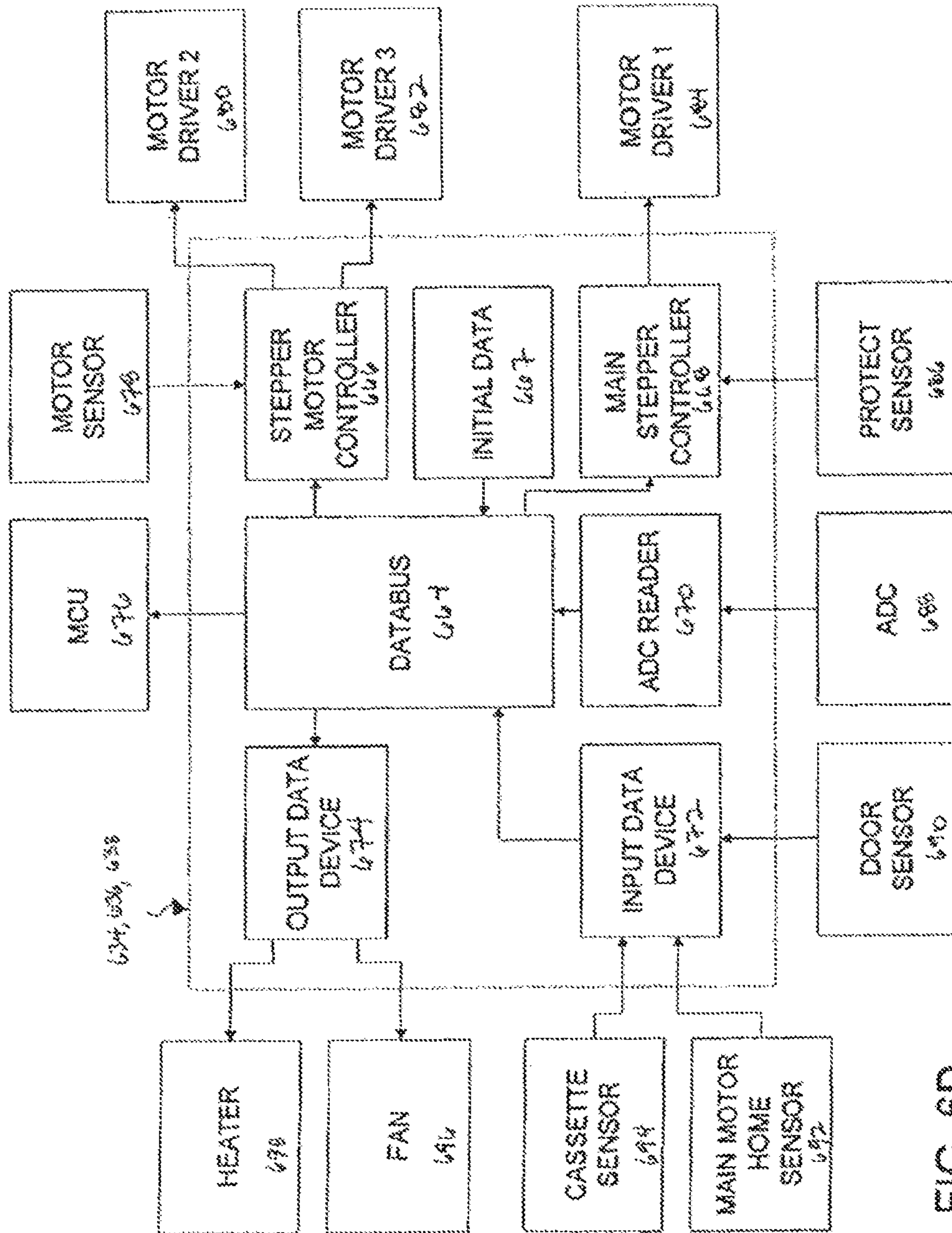


FIG. 6D

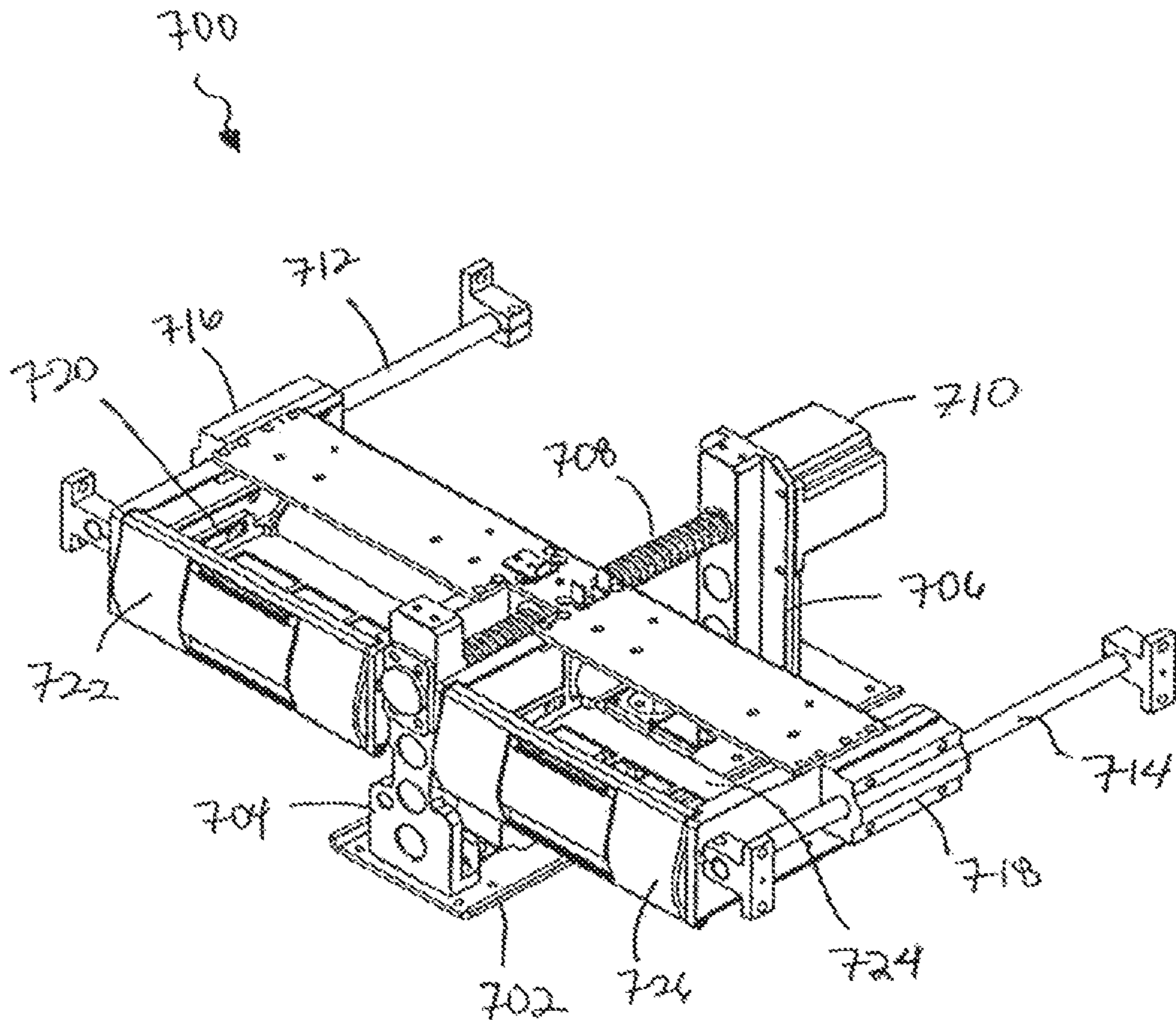


FIG. 7

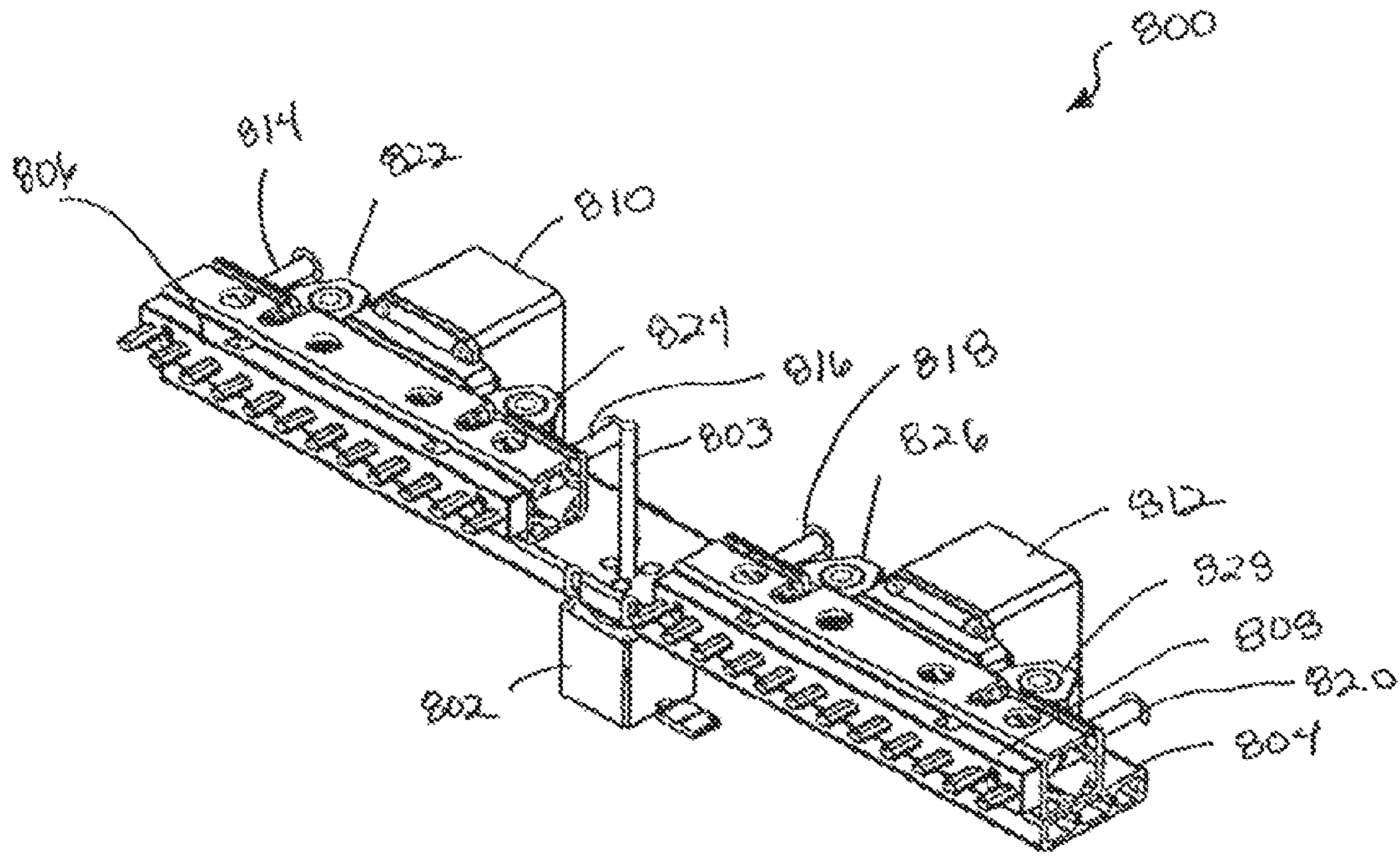


FIG. 8

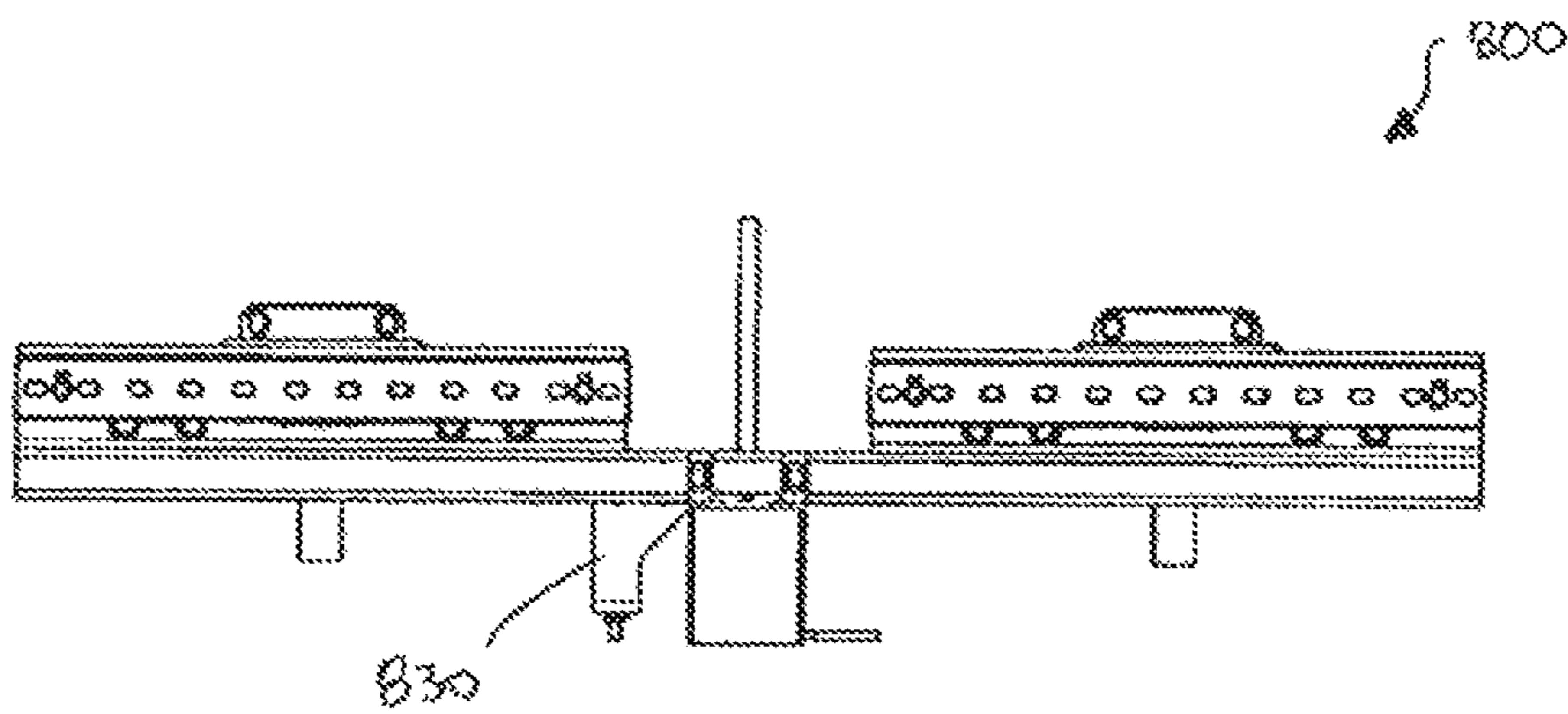


FIG. 9

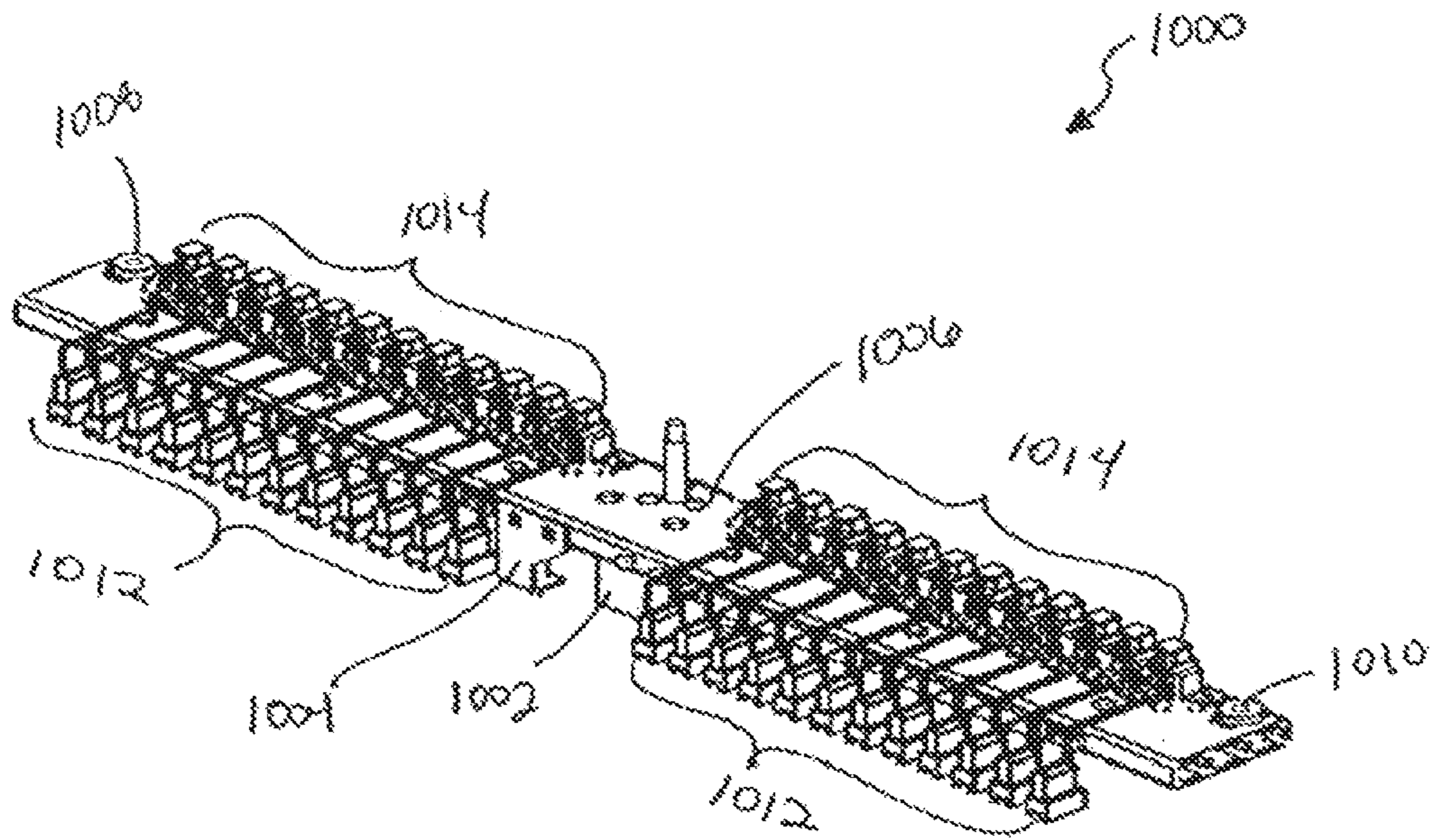


FIG. 10

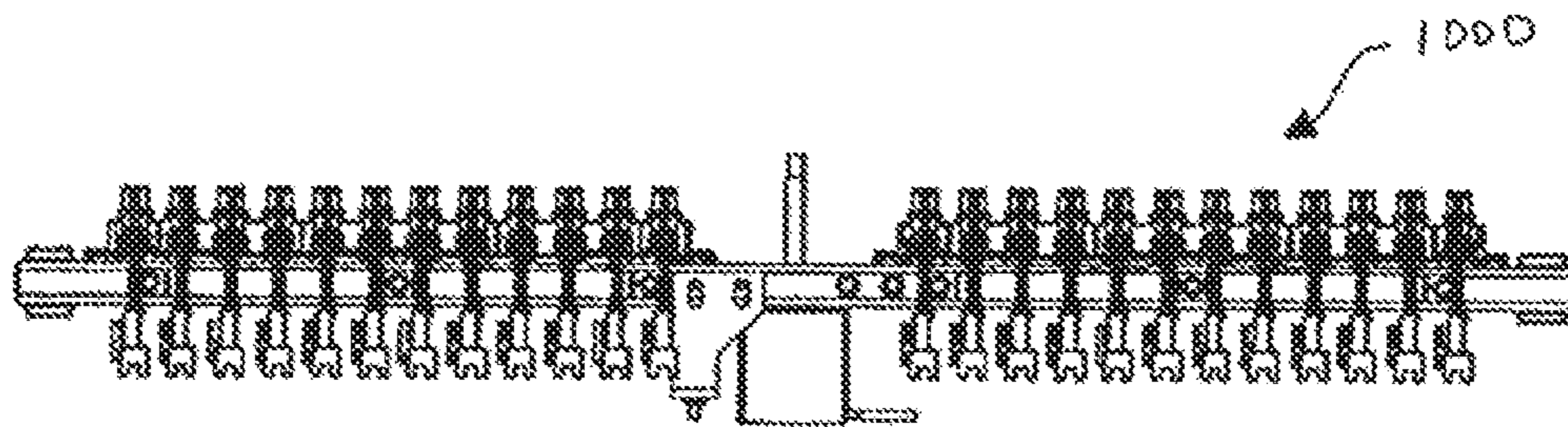


FIG. 11



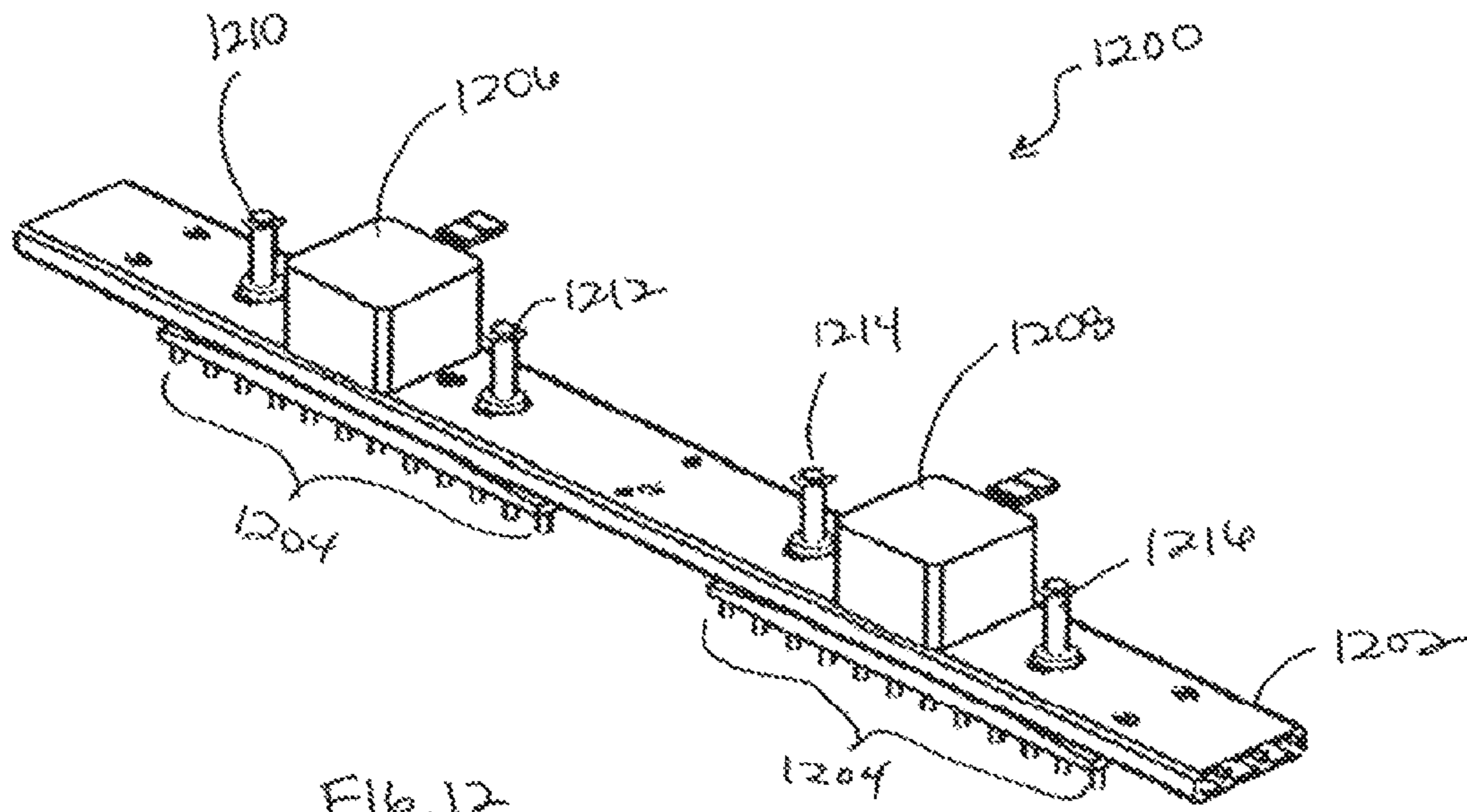


Fig. 12

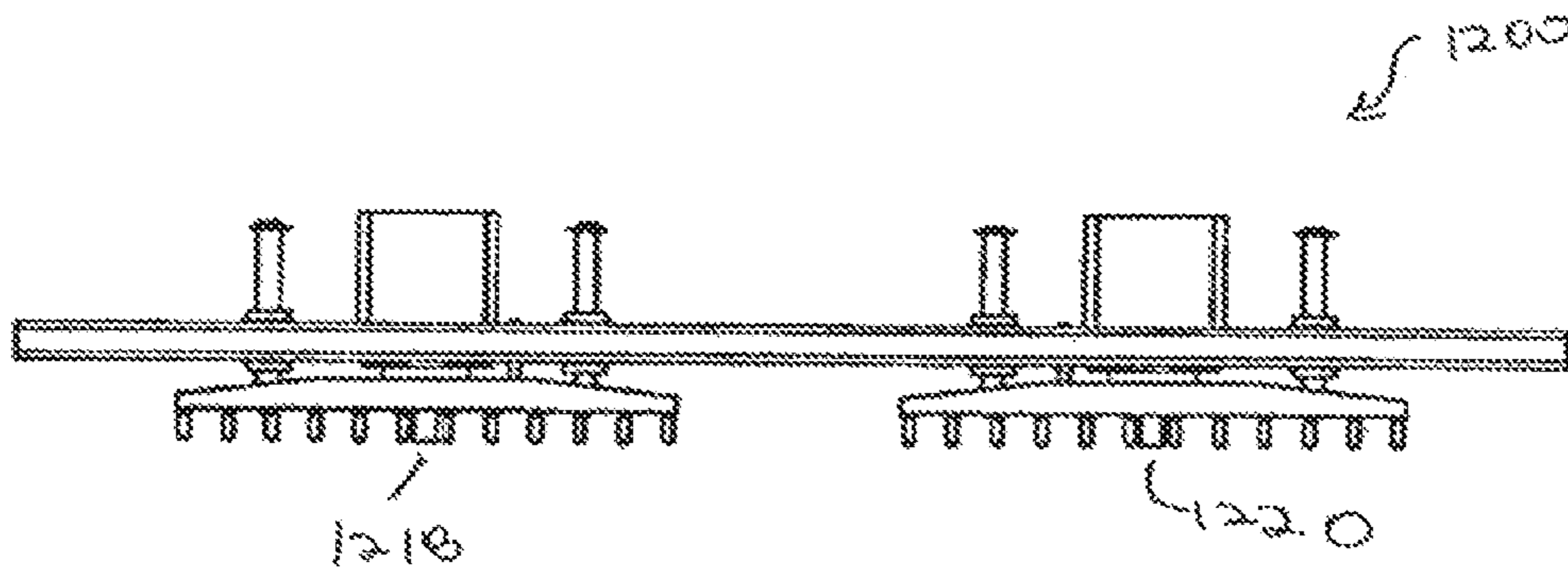


Fig. 13

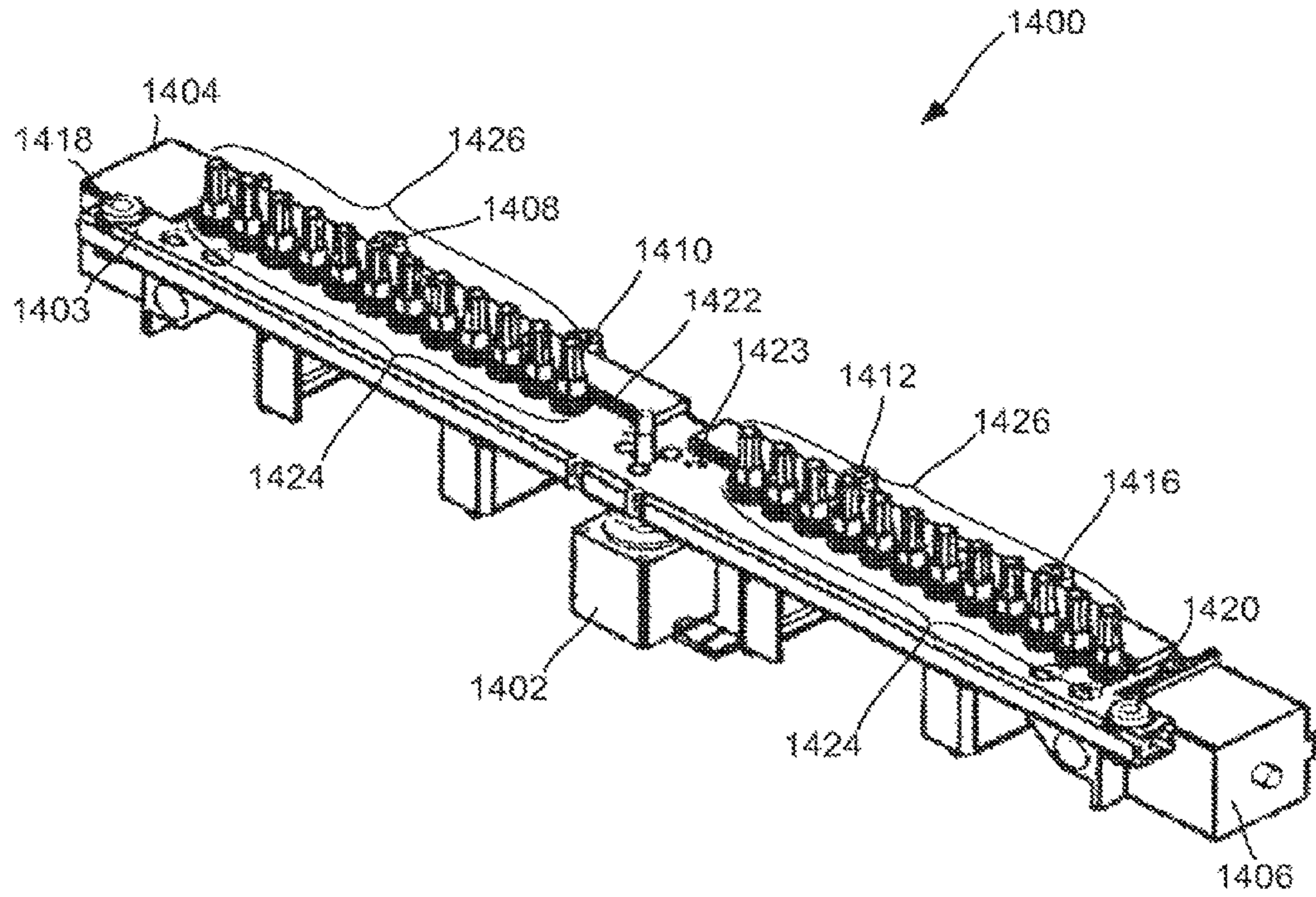


FIG. 14

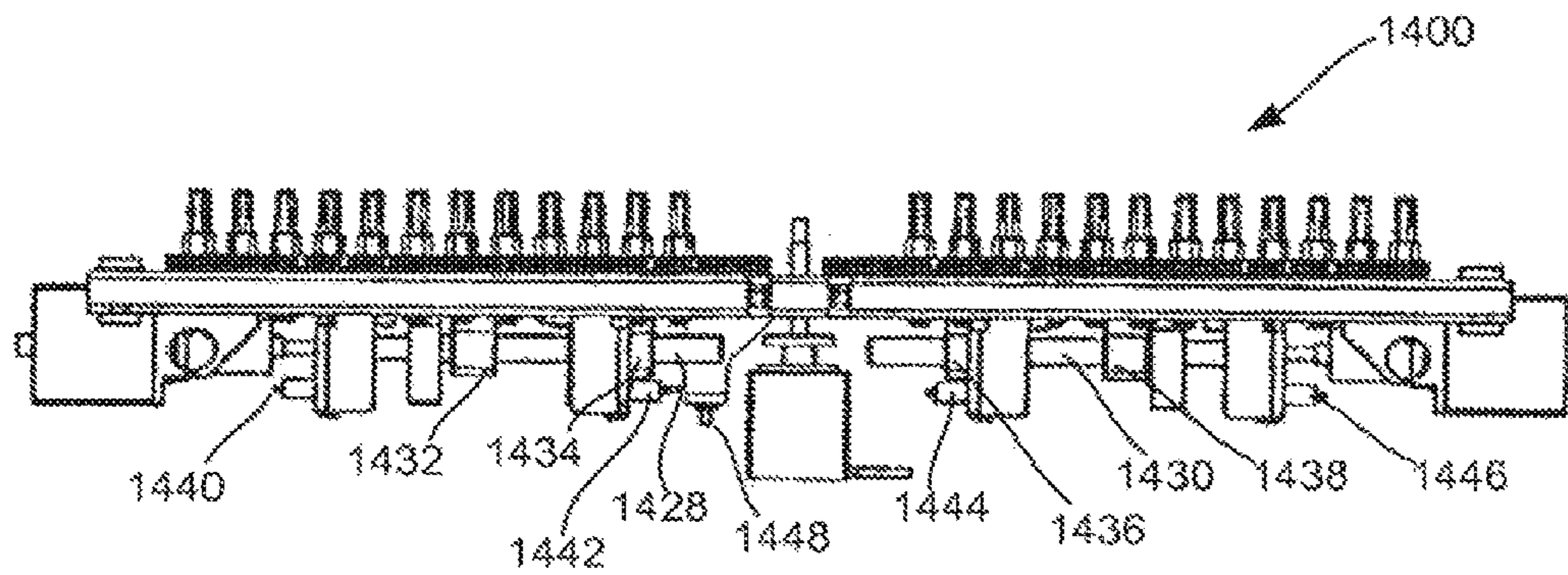


FIG. 15

## INSTRUMENT FOR CASSETTE FOR SAMPLE PREPARATION

### CROSS-REFERENCES TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/525,976, entitled "Instrument for Cassette for Sample Preparation," filed Oct. 28, 2014, which is a continuation of U.S. patent application Ser. No. 13/459,469 (now U.S. Pat. No. 8,900,877), entitled "Instrument for Cassette for Sample Preparation," filed Apr. 30, 2012, which is a continuation U.S. patent application Ser. No. 13/234,770 (now U.S. Pat. No. 8,168,443), entitled "Instrument for Cassette for Sample Preparation," filed Sep. 16, 2011, which is a continuation of U.S. patent application Ser. No. 13/044,109 (now U.S. Pat. No. 8,029,746), entitled "Instrument for Cassette for Sample Preparation," filed Mar. 9, 2011, which is a continuation of U.S. patent application Ser. No. 12/821,446 (now U.S. Pat. No. 7,910,062), entitled "Instrument for Cassette for Sample Preparation," filed Jun. 23, 2010, which is a continuation of U.S. patent application Ser. No. 12/005,860 (now U.S. Pat. No. 7,754,148), entitled "Instrument for Cassette for Sample Preparation," filed Dec. 27, 2007, which claims priority to U.S. Provisional Application Ser. No. 60/882,150, entitled "Instrument for Cassette for Sample Preparation," filed Dec. 27, 2006, each of which is incorporated herein by reference in its entirety.

### FIELD

The present invention relates to the field of biotechnology devices and, in particular, to devices and methods for preparing samples.

### BACKGROUND

DNA can be used to develop new drugs or to link someone to a crime. However, before this can be done, the DNA must be isolated from a sample. These samples include, for example, blood, urine, human cells, hair, bacteria, yeast and tissue. Each of these samples include cells, which include nucleic acid. Nucleic acid is a nucleotide chain, which conveys genetic information. The most common forms of nucleic acid are DNA and RNA.

In order to isolate the nucleic acid from the samples, prior art devices use a tray having several exposed cavities. The sample is placed into one of the cavities and conventional processing steps are used to isolate the DNA from the sample.

This prior art system has several disadvantages, including contamination, and inability to perform parallel processing or asynchronous processing. Since the cavities are exposed, contaminants can easily affect the DNA. In addition, the prior art system requires the preparation of several samples at one time. In addition, these prior art systems require a significant amount of time to process multiple samples.

### SUMMARY

In one embodiment, the present invention relates to an instrument for preparing samples. The instrument includes, for example, a parallel tray motor driving system; a close-loop heater control and detection system; a parallel magnetic particle transfer system; a parallel reagent release system; a reagent parallel pre-mix pumping system; a parallel wash buffer pumping system; and an instrument interface control-

ler to control the biological sample processing instrument that includes the parallel tray motor driving system, the close-loop heater control and detection system, the parallel magnetic particle transfer system, the parallel reagent release system, the parallel reagent pre-mix pumping system, and the parallel wash buffer pumping system.

In another embodiment, the present invention relates to a system for preparing samples. The system includes, for example, an enclosure; a parallel tray motor driving system in the enclosure to insert one or more magazines which contain one or more cassettes into the enclosure, the cassette having a sample therein; a close-loop heater control and detection system in the enclosure; a parallel magnetic particle transfer system in the enclosure; a parallel reagent release system in the enclosure; a parallel reagent pre-mix pumping system in the enclosure; and a parallel wash buffer pumping system in the enclosure.

### BRIEF DESCRIPTION OF THE DRAWINGS

The invention is described by way of example with reference to the accompanying drawings, wherein:

FIG. 1 is a perspective view of an instrument for a cassette for sample preparation in accordance with one embodiment of the invention;

FIG. 2 is a perspective view of a magazine insertable into the instrument of FIG. 1 in accordance with one embodiment of the invention;

FIG. 3 is a perspective view of a cassette for preparing samples in accordance with one embodiment of the invention;

FIG. 4 is a cross-sectional side view of the cassette for preparing samples of FIG. 3 in accordance with one embodiment of the invention;

FIG. 5 is a perspective view of an instrument for a cassette for sample preparation in accordance with one embodiment of the invention;

FIG. 6A is a block diagram of the system of the instrument of FIG. 5 in accordance with one embodiment of the invention;

FIG. 6B is a top level digital block diagram of the system controller of the instrument of FIG. 5 in accordance with one embodiment of the invention;

FIG. 6C is a digital processing block diagram of the system controller of the instrument of FIG. 5 in accordance with one embodiment of the invention;

FIG. 6D is an Instrument Module (IM) block diagram of FIG. 5 in accordance with one embodiment of the invention;

FIG. 7 is a detailed perspective view of a parallel tray driving motor assembly module in accordance with one embodiment of the invention;

FIG. 8 is a detailed perspective view of the reagent release and pre-mix assembly module in accordance with one embodiment of the invention;

FIG. 9 is a detailed side view of the reagent release and pre-mix assembly module in accordance with one embodiment of the invention;

FIG. 10 is a detailed perspective view of a close-loop heater and temperature sensor assembly module in accordance with one embodiment of the invention;

FIG. 11 is a detailed side view of the close-loop heater and temperature sensor assembly module in accordance with one embodiment of the invention;

FIG. 12 is a detailed perspective view of a parallel wash buffer pumping assembly module in accordance with one embodiment of the invention;

FIG. 13 is a detailed side view of the parallel wash buffer pumping assembly module in accordance with one embodiment of the invention;

FIG. 14 is a detailed perspective view of a parallel magnetic particles transfer assembly module in accordance with one embodiment of the invention; and

FIG. 15 is a detailed side view of the parallel magnetic particles transfer assembly module in accordance with one embodiment of the invention.

#### DETAILED DESCRIPTION

FIG. 1 illustrates an instrument 100 in accordance with one embodiment of the invention. In one embodiment, the instrument 100 is a parallel processing system.

The illustrated instrument 100 includes a display 104 and openings 108. The openings 108 are configured to receive magazines 120. The magazines 120 each contain a series of cassettes 124. Each cassette includes a sample of cells to be prepared. A protocol may be selected by a user at the display 104 for preparing the sample in the cassette 124 within the instrument 100. The instrument 100 then automatically prepares the sample within the instrument according to the selected protocol.

In the embodiment illustrated in FIG. 1, the instrument can process four magazines 120, each magazine 120 having twelve cassettes 124, each cassette having a sample of cells therein at the same time according to the selected protocol. It will be appreciated, however, that fewer than forty-eight or greater than forty-eight samples can be processed at a time.

FIG. 2 illustrates a magazine 200 in further detail. In one embodiment, the magazine 200 is the magazine 120 of FIG. 1. In one embodiment, the magazine 200 is a rack. Several cassettes 224 (e.g., cassettes 124 from FIG. 1) are placed into the magazine 200.

FIG. 3 illustrates a cassette 300 in further detail. In one embodiment, the cassette 300 is the cassettes 124 in FIG. 1 and/or cassettes 224 in FIG. 2. The cassette 300 can be used to prepare cell samples.

FIG. 4 is a detailed view of the cassette of FIG. 3. The cassette 400 includes a housing 412, a mixing chamber 414, first, second, third and fourth holding chambers 416, 418, 420 and 422, first, second, third and fourth plungers 424, 426, 428 and 430, first, second and third valves 432, 434 and 436, first and second washing chambers 438 and 440, an elution chamber 442, first, second, third and fourth pumps 444, 446, 448 and 450, first and second lids 452 and 454, first and second heating elements 456 and 458 and a magnetic 460. Each of the chambers 414, 416, 418, 420, 422, 438, 440 and 442, plungers 424, 426, 428 and 430, valves 432, 434, 436, pumps 444, 446, 448 and 450, and heating elements 456 and 458 are enclosed within the housing 412. The lids 452 and 454 are movably attached to the housing 412. The magnet 460 is removably positionable in the first valve 432, second valve 434 and third valve 436.

The mixing chamber 414 has a top surface 462, a bottom surface 464 and opposing side surfaces 466, 468. The top surface 462 of the mixing chamber 414 includes an opening 470 therein.

The first lid 452 is configured to provide access to the opening 470 in the top surface 460 of the mixing chamber 414. The first lid 452 and the opening 470 are coaxial. The first lid 452 is shown being movably attached to the housing 412, such that when the lid 452 is open or off, the opening 470 is accessible and if the lid 452 is closed or on, the opening 470 is not accessible.

A thin film 474 forms one wall of the mixing chamber 414. The thin chamber 474 is breakable, such that the mixing chamber 414 is accessible when the thin film 474 has been broken or ruptured.

The first holding chamber 416, second holding chamber 418, third holding chamber 420 and fourth holding chamber 422 are shown located next to the mixing chamber 414 and aligned vertically with one another. Each of the holding chambers 416, 418, 420, 422 has an opening 476 next to the thin film 474 of the mixing chamber 414.

The cassette 400 further includes magnetic iron particles in the form of magnetic beads in the first holding chamber 416. The cassette 400 further includes a binding solution in the second holding chamber 418. The cassette 400 further includes a lysis solution in the third holding chamber 420. The cassette 400 further includes a proteinase K (PK) solution in the fourth holding chamber 422. The magnetic iron particles (in the form of magnetic beads), lysis solution, binding solution, and proteinase K (PK) can also be provided in any chamber of the cassette 400 based on desired protocol.

The first, second, third and fourth plungers 424, 426, 428 and 430 are located in the first, second, third and fourth holding chambers 416, 418, 420 and 422, respectively.

Each of the plungers 416, 418, 420, 422 includes a base 478, a shaft 480 and a piercing element 482. The shaft 480 extends from the base 478. The piercing element 482 is at the end of the shaft 480 opposing the base 478 and is pointed. The piercing element 482 is configured to break or rupture the thin film 474 of the mixing chamber 414.

The first pump 444 is a bellows pump having a pumping portion and a nozzle portion. The nozzle portion of the first pump 444 is located inside the mixing chamber 414. The pumping portion of the first pump 444 is located outside the mixing chamber, such that the pumping portion is actuable.

A heating element 456 is provided at the bottom surface 464 of the mixing chamber 414 for heating the contents of the mixing chamber 414. The heating element 456 may be a variable heating element.

The opposing side surface 468 of the mixing chamber 414 also includes an opening 484. A first valve 432 is provided between the opening 484 in the side 468 of the mixing chamber 414 and the first washing chamber 438.

The first valve 432 has a first stationary piece 486 and a second moveable piece 488, the second piece 488 being moveable relative to the first piece 486. The first stationary piece 486 includes a first opening 490 and a second opening 492 and has a surface 494. The second piece 488 has an opening 495 therein for receiving the magnet 460. The second piece 488 has a surface 496 with a cavity 498 therein. The magnet 460 is shaped to correspond to the opening 495 in the second piece 488. The magnet 460 is moveable in the opening 495 of the second piece 488, and is removable from the second piece 488.

The cassette 400 includes a washing solution in the first washing chamber 438. The second pump 446 is also a bellows pump, and the nozzle portion of the second pump 446 is located in the first washing chamber 438.

The second valve 434 is provided between the first washing chamber 438 and the second washing chamber 440. The second valve 434 is structurally and functionally the same as the first valve 432, and also includes a first stationary piece 486 and a second moveable piece 488. The first stationary piece 486 includes a first opening 490 and a second opening 492 and has a surface 494. The second moveable piece has a surface 496 with a cavity 498 therein.

The cassette 400 includes a washing solution in the second washing chamber 440. The third pump 448 is also a bellows pump, and the nozzle portion of the third pump 448 is located in the second washing chamber 440.

The third valve 436 is provided between the second washing chamber 440 and the elution chamber 442. The third valve 436 is structurally and functionally the same as the first valve 432, and also includes a first stationary piece 486 and a second moveable piece 488. The first stationary piece 486 includes a first opening 490 and a second opening 492 and has a surface 494. The second moveable piece has a surface 496 with a cavity 498 therein.

The cassette 400 includes a washing solution in the elution chamber 442. The fourth pump 450 is also a bellows pump, and the nozzle portion of the fourth pump 450 is located in the elution chamber 442.

A heating element 458 is provided at the bottom surface of the elution chamber 442 for heating the contents of the elution chamber 442. The heating element 458 may be a variable heating element.

The elution chamber 442 includes an opening 499 at its top surface for accessing the contents of the elution chamber 442.

The second lid 442 is configured to provide access to the opening 499 in the top surface of the elution chamber 442. The second lid 454 is coaxial with the opening 499. The second lid 454 is shown being movably attached to the housing 412, such that when the lid 454 is open or off, the opening 499 is accessible and if the lid 454 is closed or on, the opening 499 is not accessible.

In use, the first lid 452 is removed to provide access to the opening 470 of the mixing chamber 414. A sample of cells is placed into the cassette 400 and, in particular, into the mixing chamber 414. The cells in the sample include nucleic acid.

The PK solution is then added to the sample. The PK solution is added by moving the plunger 430 in the fourth holding chamber 422. A force is applied to the base 478 of the plunger 430 to move the plunger 430. As the piercing element 482 of the plunger 430 advances toward the mixing chamber 414, the piercing element 482 punctures and ruptures the thin film 474. The break in the thin film 474 provides access to the mixing chamber 414. Continued motion of the plunger 430 transfers the contents (e.g., PK solution) of the first holding chamber 422 into the mixing chamber 414.

The PK solution is mixed with the sample by pumping the mixture with, for example, the first pump 444. The PK solution breaks up/destroys the walls of the cells of the sample, creating bulk material and nucleic acid in the bulk material.

The lysis solution is then added to the sample in a manner similar to the PK solution. The lysis solution is typically a salt or detergent. The lysis solution is used to solubilize the bulk material. The lysis solution typically does not solubilize proteins.

The heating element 456 may be used to heat the lysis solution and sample. As described hereinabove, the temperature of the heating element 456 may be variable, and is selected to optimize the effectiveness of the lysis solution.

The binding solution is then added to the sample, PK solution and lysis buffer solution. The binding solution is typically hydrophobic and increases salt in the solution. The binding solution causes the nucleic acid to be magnetically charged.

The magnetic beads are then added to the solution and pumped. The magnetic beads bind to the magnetically charged nucleic acid.

The magnetic beads, together with the nucleic acid, are bound to the first valve 432. The removable positionable magnet 460 is placed in the first valve 432 and slid to a position in the first valve 432 to attract the magnetic beads, which are bound to the nucleic acid, from the mixing chamber 414 to the first valve 432.

The magnetic beads, together with the nucleic acid, are then moved from the mixing chamber 414 and received in the first washing chamber 438.

The magnet 460 is inserted into the opening 494 of the second piece 488. The magnet 460 is inserted to a position corresponding to the openings 490 and 492 of the first piece 486. The magnet 460 attracts the magnetic beads from the mixing chamber 414 through the opening 490 in the first piece 486 and into the cavity 498 in the second piece 488. The second piece 488 is rotated such that the magnetic beads are sealed in the cavity 498 of the second piece 488, between surfaces of the second piece 488 and the first piece 486. The second piece 488 is rotated past the surface 494 of the first piece 486, such that the cavity 498 is accessible in the opening 492 of the first piece 486. The magnet 460 is then removed from the opening 494 in the second piece 488 to release the magnetic beads from the cavity 498 in the second piece 488.

The magnetic beads and nucleic acid are then washed with the washing solution by pumping the solution with the second pump 446. The magnetic beads, together with the nucleic acid, are then bound to the second valve 434 by inserting the magnet 460 into the second valve 434.

The magnetic beads, together with the nucleic acid, are then moved from the first washing chamber 438 to the second washing chamber 440 using the second valve 434. The second valve 434 transfers the magnetic beads and nucleic acid from the first washing chamber 438 to the second washing chamber 440.

The magnetic beads and nucleic acid are then washed with the washing solution a second time by pumping the solution with the third pump 448. The magnetic beads, together with the nucleic acid, are then bound to the third valve 436 by positioning the magnet 460 in the third valve 436.

The magnetic beads and nucleic acid are then moved from the second washing chamber 440 to the elution chamber 442. The magnetic beads and nucleic acid are transferred from the second washing chamber 440 to the elution chamber 442.

An elution buffer solution is then mixed with the magnetic beads and nucleic acid by pumping the solution with the fourth pump 450. The heating element 458 may be used to heat the elution buffer, magnetic beads and nucleic acid. The temperature may be variable and may be selected to optimize release of the nucleic acid from the magnetic beads.

The magnetic beads alone are then bound again to the third valve 436 by positioning the magnet 460 in the third valve 436.

The magnetic beads alone are then moved from the elution chamber 442 back into the second washing chamber 440, leaving the nucleic acid in the elution chamber 442. The magnetic beads are transferred from the elution chamber 442 to the second washing chamber 440.

The prepared sample of nucleic acid may be accessed from the opening 499 in the elution chamber 442. The second lid 54 is removed to provide access to the opening 499 in the elution chamber 42.

In one embodiment, a pipette or a multi-channel pipette may be used to place the sample in the cassette and/or access the sample or a plurality of samples in the cassette(s).

It will be appreciated that the cassette may vary from that illustrated and described above. For example, seals may be provided in the cassette as need. In another example, although the cassette **400** has been described as having a mixing chamber **414**, two washing chambers **438** and **440** and an elution chamber **442**, it is envisioned that only one washing chamber or no washing chamber may alternatively be provided.

In another example, the valves may have a different arrangement than that described above. In another example, although the cassette has been described as using a single removable magnet **460**, it is envisioned that each valve may include a positionable magnet, such that the magnet does not need to be removed. The magnet **460** may be rotatable, and used to rotate the second piece of the valves. Alternatively, the magnet may only slide inside of each of the valves, and the second piece is rotated independent of the magnet. It is envisioned that a cassette **400** that does not use valves as described herein may be used to transfer the magnetic particles from the mixing chamber to the elution chamber. In such an embodiment, a slideable magnet may be provided to transfer the magnetic particles from one chamber to the next.

It is envisioned that the housing **412** may be transparent, such that the procedure can be viewed. In one embodiment the thin film **474** is a lamination. In one embodiment, the lids **452** and **454** may be screw-top lids. In one embodiment, the lids **452**, **454** include a hydrophobic membrane, which allows gasses to vent through the lid, but does not allow the liquids to escape the cassette **400**. In one embodiment, pump **450** is insertable into opening **499**. In one embodiment, pump **450** can also be used as a pipette to remove the sample from the cassette **400**. It is also envisioned that the mixing chamber **414** may be provided without a puncturable thin film **474**. In such an embodiment, the plungers **424**, **426**, **428** and **430** would not need a piercing element **482**. Instead, the plungers **424**, **426**, **428** and **430** would have a sealing element to prevent leakage of the contents of the holding chamber **416**, **418**, **420** and **422**, associated with each plunger **424**, **426**, **428** and **430**, respectively, until the plunger was moved.

In one embodiment, a total of about 200  $\mu\text{L}$  sample is placed into the cassette. The sample is mixed with a total of about 50  $\mu\text{L}$  of the PK solution by pumping the mixture of the sample and PK solution for about one minute. A total of about 200  $\mu\text{L}$  of the lysis solution is added to the sample and PK solution, and the solutions are pumped for about one minute to mix the solutions. The mixture is then heated at about 60° C. for about ten minutes, and the mixture is allowed to cool for about 5 minutes. The mixture is further pumped while it cools. A total of about 500  $\mu\text{L}$  of binding solution is added to the mixture. The solutions are pumped for about one minute. The magnetic beads are added to the solution and pumped for about two minutes. The magnetic beads are transferred and washed as described above. A total of about 700  $\mu\text{L}$  of washing solution is provided in each of the washing chambers. A total of about 200  $\mu\text{L}$  of elution solution is provided in the elution chamber. The magnetic beads are mixed with the elution solution by pumping the mixture for about one minute. The mixture is then heated at about 90° C. for about two minutes. The process continues as previously described. It will be appreciated that the amounts, times and temperatures described above may vary from that described above.

Although the cassette **400** has been described as using a PK solution, lysis solution, binding solution and magnetic beads to release the nucleic acid and magnetic beads, it is envisioned that it may be possible to practice the invention without using each of the above solutions. In addition, although the solution was described as using a PK solution to break up the cells, it is envisioned that any enzyme which causes cells to break up to release nucleic acid may be used with the invention. Furthermore, it will be appreciated that additional solutions may be provided, as needed, to prepare the sample. One of skill in the art will also understand that the cassette **400** may be modified to have fewer holding chambers if fewer solutions are used or additional holding chambers if additional solutions are used.

FIG. **5** illustrates another embodiment of an instrument **500** in accordance with one embodiment of the invention. It will be appreciated that the magazine and cassettes described herein with reference to FIGS. **2-4** can be used with the instrument **500**. The instrument **500** allows for parallel processing of one or more samples within a closed, sterile environment.

Instrument **500** includes an enclosure **502**, an instrument handle **504**, stackable holders **506**, an instrument module **508**, a computer module **510**, a touch panel display **512**, an instrument run time indicator **514**, first and second automatic eject/load trays **516**, **518**, first and second tray doors **520**, **522**, and first and second tray safety guards **524**, **526**.

The instrument module **508** is within the enclosure **502** and is configured to perform the protocol selected to prepare the sample. The protocol is selected by the user using the touch screen display **512**. In one embodiment, the display **512** is a touch screen display. For example, the display **512** may be, for example, a 7" to 12" touch screen LCD display. The user's selection at the display **512** is communicated to the computer module **510** which communicates with the instrument module **508** via a controller area network bus (CAN-BUS) to coordinate processing within the instrument **500**.

The stackable holders **506** enable multiple instruments **500** to be stacked on top of one another such that even more samples can be processed at any given time. In one embodiment, one computer module **510** and display **512** may be provided to control processing within multiple stacked instruments.

The first and second automatic eject/load trays **516**, **518** are configured to receive a magazine (e.g., magazine **200**) having one or more cassettes therein (e.g., cassette **400**). The magazines are automatically loaded into the instrument **500** by the automatic eject/load trays **516**, **518**. The first and second cassette doors **520**, **522** are closed and engage with the first and second tray safety guards **524**, **526** to secure the magazine and cassettes within the enclosure **502** of the instrument **500** for preparation of the sample. It will be appreciated that in alternative embodiments the trays **516**, **518** and/or doors **520**, **522** may be manually opened and closed.

In one embodiment, the instrument run time indicator **514** is an LED or other exemplary light source. The instrument run time indicator **514** is illuminated to indicate to a user about the instrument ID and run status. In one embodiment, the computer module **510** provides an indication to the instrument run time indicator **514** to illuminate the communication status between the controller and the instrument.

FIG. **6A** is a block diagram of the system components **600** of the instrument **500**. The system components **600** include, a main computer **602**, a display panel **604**, a sub-system computer **606**, an instrument interface parallel controller

608, an instrument real time microcontroller unit (MCU) 610, a cooling system 612, a tray motor driving system 614, a heater control and detection system 616, a magnetic particle transfer system 618, a reagent release system 620, a reagent pre-mix pumping system 622 and a wash buffer pumping system 624.

Each of the cooling system 612, tray motor driving system 614, heater control and detection system 616, magnetic particle transfer system 618, reagent release system 620, reagent pre-mix pumping system 622 and wash buffer pumping system 624 communicate with the instrument interface parallel controller 608. In one embodiment, the instrument interface parallel controller is configured to control the subsystems 612-624 such that up to twenty-four samples can be prepared at a given time. It will be appreciated, however, that the instrument can be configured to prepare fewer than or greater than twenty-four samples. It will be appreciated that the system components 600 communicate with one another to enable parallel processing of the sample(s) within the instrument 500.

The instrument interface parallel controller 608 also communicates with the instrument real time MCU 610, the cooling system 612 and the sub-system computer 606. The sub-system computer 606 communicates with the main computer 602. The main computer 602 communicates with the touch screen display panel 604.

In one embodiment, the main computer 602, sub-system computer 606, and/or the instrument interface parallel controller 608 are a digital processing system. The digital processing system may include a microprocessor, an ASIC (application specific integrated circuit), FPGA (field-programmable gate array), DSP (digital signal processor), or the like. In one embodiment, the display panel 604 is a 7" high definition (HD) liquid crystal display (LCD) with a touch panel. The display panel 604 is on an external surface of the instrument 500 such that the user can interact with the display panel 604. The main computer 602 may be a stand alone system that includes the computer module 510 and display 512. The sub-system computer 606 and instrument interface parallel controller 608 are within the enclosure 502 of the instrument 500. As described above with reference to FIG. 5, the user can select a protocol for processing the sample(s) with the display panel 604. The display panel 604 communicates the user selection to the main computer 602, sub-system computer 606 and/or parallel controller 608 to perform the protocol using the tray motor driving system 614, heater control and detection system 616, magnetic particle transfer system 618, reagent release system 620, reagent pre-mix pumping system 622 and wash buffer pumping system 624.

In one embodiment, the tray motor driving system 614 is configured to control the automatic load/eject trays 516, 518 (from FIG. 5) and cassette doors 520, 522 to automatically load the cassettes (e.g., cassette 400) for processing and eject the cassettes when processing of the sample is completed.

In one embodiment, the heater control and detection system 616 is configured to control and detect the temperature of the cassette or cassettes. The heater control and detection system may also control the heaters within the cassette to perform a close loop temperature ramping and detection. Alternatively or in addition to controlling the heaters within the cassette, the heater control and detection system 614 may include heaters that are configured as a programmable temperature controller to heat the contents of the cassette to a predefined temperature, as needed, according to the selected protocol.

In one embodiment, the magnetic particle transfer system 618 is configured to transfer magnetic particles within the cassette (e.g., cassette 400) according to the selected protocol. In one embodiment, the magnetic particle transfer system 618 manipulates the valves 432, 434, 436 to transfer the magnetic particles as described above with reference to FIG. 4.

In one embodiment, the reagent release system 620 is configured to release the reagents within the cassette. For example, the reagent release system is configured to release the PK solution, lysis solution, binding solution and magnetic beads from their respective holding chambers 416, 418, 420 and 422 and into the mixing chamber 414, as described above with reference to FIG. 4.

In one embodiment, the reagent pre-mix pumping system 622 is configured to mix the reagents in the mixing chamber 414 as described above with reference to FIG. 4.

In one embodiment, the wash buffer pumping system 624 is configured to pump the washing solution in the cassette, as described above with reference to FIG. 4. For example, the wash buffer pumping system 624 may be configured to actuate the pumps 446, 448, 450 in the wash chambers 438, 440 and elution chamber 442.

FIG. 6B illustrates a block diagram of a digital system 630 in accordance with one embodiment of the invention. The illustrated digital system 630 includes a system controller module (SCM) 632, a first instrument module (IM) 1 634, a second instrument module (IM) 2 636 and a nth instrument module (IM) N 638. The SCM 632 controls each of the IM 1 634, IM 2 636 and up to an nth IM N 638. It will be appreciated that the SCM 632 may control any number of IMs as represented by N. Thus, N may be any number from 0 up to 100 or even more.

FIG. 6C is a block diagram illustrating the system controller module 632 of FIG. 6B in further detail. The system controller module 632 includes a main processor unit 640, a Complex Programmable Logic Device (CPLD) 642, a Liquid Crystal Display (LCD) 644, a Synchronous Dynamic Random Access Memory (SDRAM) 646, a NOR flash 648, a NAND flash 650, a Storage Device (SD) card 652, a Universal Asynchronous Receiver-Transmitter (UART) 654, a CANBUS 656, a Universal Serial Bus (USB) 658, an Ethernet 660 and a system bus 662 to couple each of the components 640-662.

The bus 662 or other internal communication means is for communicating information, and the main processor unit 640 is coupled to the bus 662 for processing information. SDRAM 646, NOR flash 648, NAND flash 650, and SD card 652 (referred to as memory) are for storing information and instructions to be executed by the main processor unit 640, for storing temporary variables or other intermediate information during execution of instructions by main processor unit 640, for storing static information and instructions for main processor unit 640, and the like.

The system may further be coupled to a display device, such as a cathode ray tube (CRT) or a liquid crystal display (LCD) 644, coupled to bus 662 through bus 662 for displaying information to a computer user. An alphanumeric input device 675, including alphanumeric and other keys, may also be coupled to bus 662 through bus 662 for communicating information and command selections to the main processor unit 640. An additional user input device is cursor control device, such as a mouse, a trackball, stylus, or cursor direction keys coupled to bus 662 through bus 662 for communicating direction information and command selections to main processor unit 640, and for controlling cursor movement on display device 644.

## 11

Another device, which may optionally be coupled to computer system, is a communication device, such as UART **654**, CANBUS **656**, USB **658**, and Ethernet **660**, for accessing other nodes of a distributed system via a network. The communication device may include any of a number of commercially available networking peripheral devices such as those used for coupling to an Ethernet, token ring, Internet, control area network (CAN), wide area network (WAN), and wireless network (WIFI). The communication device may further be a null-modem connection via UART, or any other mechanism that provides connectivity between the computer system and the outside world, or any other mechanism that provides connectivity between the controller computer system and instrument modules. Note that any or all of the components of this system illustrated in FIG. 6C and associated hardware may be used in various embodiments of the present invention.

It will be appreciated by those of ordinary skill in the art that any configuration of the system may be used for various purposes according to the particular implementation. The control logic or software implementing the present invention can be stored in SDRAM **646**, NOR Flash **648**, NAND flash **650**, SD card **652**, FPGA, CPLD or other storage medium locally or remotely accessible to main processor unit **640**.

It will be apparent to those of ordinary skill in the art that the system, method, and process described herein can be implemented as software stored in memory and executed by main processor unit **640**. This control logic or software may also be resident on an article of manufacture comprising a computer readable medium having computer readable program code embodied therein and being readable by the storage device and for causing the main processor unit **640** to operate in accordance with the methods and teachings herein.

The present invention may also be embodied in a handheld or portable device containing a subset of the computer hardware components described above. For example, the handheld device may be configured to contain only the bus **662**, the main processor unit **640**, and SDRAM **646**. The handheld device may also be configured to include a set of buttons or input signaling components with which a user may select from a set of available options. The handheld device may also be configured to include an output apparatus such as a liquid crystal display (LCD) or display element matrix for displaying information to a user of the handheld device. Conventional methods may be used to implement such a handheld device. The implementation of the present invention for such a device would be apparent to one of ordinary skill in the art given the disclosure of the present invention as provided herein.

The present invention may also be embodied in a special purpose appliance including a subset of the computer hardware components described above. For example, the appliance may include a main processor unit **640**, SDRAM **646** and bus **662**, and only rudimentary communications mechanisms, such as a small touch-screen that permits the user to communicate in a basic manner with the device. In general, the more special-purpose the device is, the fewer of the elements need to be presented for the device to function. In some devices, communications with the user may be through a touch-based screen, USB devices, or similar mechanism.

It will be appreciated by those of ordinary skill in the art that any configuration of the system may be used for various purposes according to the particular implementation. The control logic or software implementing the present invention can be stored on any machine-readable medium locally or

## 12

remotely accessible to processor. A machine-readable medium includes any mechanism for storing or transmitting information in a form readable by a machine (e.g. a computer). For example, a machine readable medium includes read-only memory (ROM), random access memory (RAM), magnetic disk storage media, optical storage media, flash memory devices, electrical, optical, acoustical or other forms of propagated signals (e.g. carrier waves, infrared signals, digital signals, etc.).

FIG. 6D is a block diagram illustrating the instrument modules **634**, **636**, **638** of FIG. 6B in further detail. The instrument modules **634**, **636**, **638** include a databus **664**, a stepper motor controller **666**, initial data **667**, a main stepper controller **668**, an ADC reader **670**, an input data device **672** and an output data device **674**. The stepper motor controller **666**, initial data **666**, main stepper controller **668**, Analog-to-Digital Converter (ADC) reader **670**, input data device **672** and output data device **674** are each coupled to the databus **664**.

In the embodiment illustrated in FIG. 6D, the instrument module is shown for the tray motor driving module of FIG. 6A. It will be appreciated that the instrument modules for the other modules of FIG. 6A will have similar components as the illustrated instrument module; however, the inputs and outputs coupled with the instrument modules may vary.

The illustrated databus **664** is also coupled with a MCU **676**. The stepper motor controller **666** is also coupled with the motor sensor **678**, motor driver **2 680** and motor driver **3 682**. The main stepper controller **668** is also coupled with the motor driver **1 684** and protect sensor **686**. The ADC reader **670** is also coupled with the ADC **688**. The input data device **672** is also coupled with the door sensor **690**, main motor home sensor **692**, and cassette sensor **694**. The output data device **674** is also coupled with the fan **696** and the heater **698**.

FIG. 7 illustrates a tray driving motor assembly module **700**. In one embodiment, the tray driving motor assembly module **700** is part of the tray motor driving system **614** of FIG. 6. In one embodiment, the tray driving motor assembly module **700** is within the instrument module **508** of the instrument **500** as described above with reference to FIG. 5.

The tray driving motor assembly module **700** includes an alignment plate **702**, a first drive shaft retention block **704**, a second drive shaft retention block **706**, a load driving shaft **708**, a main driving motor **710**, a first parallel shaft **712**, a second parallel shaft **714**, a first parallel linear drive **716**, a second parallel linear drive **718**, a first load resistance tray **720**, a first door **722**, a second load resistance tray **724** and a second door **726**.

The main drive motor **710** is coupled with the load driving shaft **708** via the retention blocks **704**, **706** to automatically load and eject the rack trays **720**, **724** into the instrument. The trays **720**, **724** also slide along the parallel shafts **712**, **714** with the main drive motor **710** and the drives **716**, **718** to load and eject the racks **720**, **724**. The motor **710** and/or drivers **712**, **714** can also be used to open and close the doors **722**, **726**.

FIG. 8 illustrates a reagent release and pre-mix assembly module **800**. In one embodiment, the reagent release and pre-mix assembly module **800** is part of the reagent release system **620** and reagent pre-mix pumping system **622**. In one embodiment, the reagent release and pre-mix assembly module **800** is within the instrument module **508** of the instrument **500** as described above with reference to FIG. 5.

The reagent release and pre-mix assembly module **800** includes a precision vertical engagement driving motor **802**, a vertical drive shaft **803**, a stand **804**, a first plunger



assembly **806**, a second plunger assembly **808**, a first parallel horizontal pump activation motor **810**, a second parallel horizontal pump activation motor **812**, first, second, third and fourth horizontal parallel linear driving shafts and bearings **814**, **816**, **818** and **820**, and first, second, third and fourth vertical parallel linear bearings **822**, **824**, **826** and **828**.

In one particular embodiment, each of the plunger assemblies **806**, **808** includes twelve plungers (e.g., one plunger for each cassette in the magazine). It will be appreciated that the plunger assemblies **806**, **808** may have fewer than or greater than twelve plungers.

FIG. **9** is a side view of reagent release and pre-mix assembly module **800** of FIG. **8**. As shown in FIG. **9**, the reagent release and pre-mix assembly module **800** of FIG. **8** also includes a vertical position sensor **830**.

With reference to FIGS. **8** and **9**, the stand **804** is coupled with the vertical drive shaft **803**, which is coupled with the vertical engagement driving motor **802** to vertically position the stand **804**. The plunger assemblies **806**, **808** are coupled with the stand **804** and are, thus, also vertically positioned with the stand **804** when the motor **802** is actuated. The vertical position sensor **830** is coupled with the stand **804** to sense the position of the stand **804** and/or plunger assemblies **806**, **808**. The vertical position sensor **830** communicates with a controller to control actuation of the motor **802**. The plunger assemblies **806**, **808** are also actuatable horizontally via the horizontal drive shafts and bearings **814-820**, which are coupled with the horizontal motors **810**, **812**.

The plunger assemblies **806**, **808** are actuated in a vertical direction to align the plungers **806**, **808** with one of the holding chambers of the cassette **400**. The plunger assemblies **806**, **808** are also actuated horizontally to force the contents of the holding chambers into the mixing chamber of the cassette **400**. The plunger assemblies **806**, **808** are then repositioned vertically to align with another holding chamber and are similarly actuated horizontally to force the contents of the holding chamber into the mixing chamber according to the selected protocol. In one embodiment, the plunger assemblies **806**, **808** are also actuated to actuate the pump **444** that mixes the contents of the mixing chamber of the cassette **400**.

FIGS. **10** and **11** illustrate a heater and temperature sensor assembly module **1000**. In one embodiment, the heater and temperature sensor assembly module **1000** is part of the heater control and detection system **616**. In one embodiment, the heater and temperature sensor assembly module **1000** is within the instrument module **508** of the instrument **500** as described above with reference to FIG. **5**.

The heater and temperature sensor assembly module **1000** includes a precision vertical engagement driving motor **1002**, a vertical position sensor **1004**, a rack **1006**, a first vertical linear bearing **1008**, a second vertical linear bearing **1010**, a plurality of heater and thermal sensor connectors **1012** and a plurality of individually controlled parallel heaters and thermal sensors **1014**. In one embodiment, the plurality of individually controlled parallel heaters and thermal sensors **1014** are self-aligned with the plurality of heater and thermal sensor connectors **1012**.

In one particular embodiment, the heater and temperature sensor assembly module **1000** includes twenty-four heater and thermal sensor connectors **1012** and twenty-four individually controlled parallel heaters and thermal sensors **1014**. It will be appreciated that the heater and temperature sensor assembly module **1000** may include fewer than or greater than twenty-four connectors **1012** and/or heaters/sensors **1014**.

The vertical linear bearings **1008**, **1010** are coupled with the vertical engagement driving motor **1002** to vertically position the rack **1006**. The plurality of heater and thermal sensor connectors **1012** and plurality of individually controlled parallel heaters and thermal sensors **1014** are coupled with respective sides of the rack **1006**. The plurality of heater and thermal sensor connectors **1012** and plurality of individually controlled parallel heaters and thermal sensors **1014** are vertically positionable by vertically positioning the rack **1006**. The vertical precision position sensor **1004**, coupled with the rack **1006**, can be used to accurately position the plurality of heater and thermal sensor connectors **1012** and plurality of individually controlled parallel heaters and thermal sensors **1014**.

FIGS. **12** and **13** illustrate a wash buffer pumping assembly module **1200**. In one embodiment, the wash buffer pumping assembly module **1200** is part of the wash buffer pumping system **624**. In one embodiment, the wash buffer pumping assembly module **1200** is within the instrument module **508** of the instrument **500** as described above with reference to FIG. **5**.

The wash buffer pumping assembly module **1200** includes a rack **1202**, a plurality of parallel vertical pump engagement plungers **1204**, a first parallel vertical pump activation motor **1206**, a second parallel vertical pump activation motor **1208**, and first, second, third and fourth vertical parallel linear driving shafts and bearings **1210**, **1212**, **1214** and **1216**. As shown in FIG. **13**, the wash buffer pumping assembly module **1200** also includes first and second vertical precision position sensors **1218** and **1220**.

The first vertical pump activation motor **1206** is coupled with the first and second vertical parallel linear driving shafts and bearings **1210**, **1212** to vertically position a first set of parallel vertical pump engagement plungers **1204a**. Similarly, the second vertical pump activation motor **1206** is coupled with the third and fourth vertical parallel linear driving shafts and bearings **1214**, **1216** to vertically position a second set of parallel vertical pump engagement plungers **1204b**.

The plungers from the vertical pump engagement plungers **1204** engage with the cassette (e.g., cassette **400**) to actuate the pumps **446**, **448**, **450** in the wash chambers **438**, **440** and elution chamber **442** according to the selected protocol.

FIGS. **14** and **15** illustrate a magnetic particles transfer assembly module **1400**. In one embodiment, the magnetic particles transfer assembly module **1400** is part of the magnetic particle transfer system **618**. In one embodiment, the magnetic particles transfer assembly module **1400** is within the instrument module **508** of the instrument **500** as described above with reference to FIG. **5**.

The magnetic particles transfer assembly module **1400** includes a rack **1402**, a precision vertical engagement driving motor **1402**, a first particle transfer linear motor **1404**, a second particle transfer linear motor **1406**, first, second, third and fourth gear rack retention roller bearings **1408**, **1410**, **1412** and **1416**, first and second vertical linear bearings **1418** and **1420**, first and second driving gear racks **1422**, **1423**, a plurality of parallel precision gears **1424** and a plurality of parallel magnets and valve key shafts **1426**. As shown in FIG. **15**, the magnetic particles transfer assembly module **1400** also includes first and second linear driving shafts **1428** and **1430**, first, second, third and fourth shaft and gear rack link blocks **1432**, **1434**, **1436** and **1438**, first, second, third and fourth horizontal precision position sensors **1440**, **1442**, **1444** and **1446**, and a vertical precision position sensor **1448**.

In one particular embodiment, the magnetic particles transfer assembly module **1400** includes twenty-four parallel precision gears **1424** and twenty-four parallel magnets and valve key shafts **1426**. It will be appreciated that the magnetic particles transfer assembly module **1400** may have fewer than or greater than twenty-four gears **1424** and magnets and key shafts **1426**.

The precision vertical engagement driving motor **1402** is coupled with vertical bearings **1418**, **1420** and the rack **1403** to vertically position the rack **1403**. The plurality of parallel magnets and valve key shafts **1426** are positioned on the rack **1403** and are vertically positioned when the rack **1403** is vertically positioned. The vertical precision position sensor **1448** is coupled with the rack **1403** and motor **1402** to accurately position the plurality of parallel magnets and valve key shafts **1426** in the cassette (e.g., cassette **400**).

The particle transfer linear motors **1404**, **1405** are positioned on either end of the rack **1403** and are coupled with the linear driving shafts **1428**, **1430**, shaft and gear rack link blocks **1432-1438**, driving gear racks **1422**, gears **1424**, to horizontally position and rotate the plurality of parallel magnets and valve key shafts **1426** via the gears **1424** to transfer magnetic particles as described above with reference to FIG. **4**. It will be appreciated that the gears **1424** and magnets and shafts **1426** can be repositioned to transfer the particles with each valve of the cassette.

The foregoing description with attached drawings is only illustrative of possible embodiments of the described method and should only be construed as such. Other persons of ordinary skill in the art will realize that many other specific embodiments are possible that fall within the scope and spirit of the present idea. The scope of the invention is indicated by the following claims rather than by the foregoing description. Any and all modifications which come within the meaning and range of equivalency of the following claims are to be considered within their scope.

The invention claimed is:

1. A system comprising:
  - a network; and
  - a plurality of instruments, wherein:
    - each instrument in the plurality of instruments is configured to receive a plurality of cassettes;
    - each instrument in the plurality of instruments comprises a particle transfer system including a plurality of valve shafts and a first actuator assembly;
    - each instrument in the plurality of instruments comprises a computer; and
    - each instrument in the plurality of instruments comprises a communication device, wherein the communication device is configured to couple the instrument to the network;
  - wherein the first actuator assembly is configured to move the plurality of valve shafts between a first position and a second position; and
  - the first actuator assembly is configured to rotate each valve shaft from the plurality of valve shafts when the plurality of valve shafts is in the second position.
2. The system of claim **1** wherein each cassette of the plurality of cassettes comprises a valve member defining a cavity within which a particle can be disposed, the valve member configured to transfer the particle between a first chamber of the cassette and a second chamber of the cassette.
3. The system of claim **2** wherein the first actuator assembly is configured to apply a magnetic force produced by a magnetic portion of each valve shaft to attract the

particle into the cavity of the valve member of the corresponding cassette from the plurality of cassettes.

4. The system of claim **3** wherein the first actuator assembly is configured to rotate when the particle is transferred between the first chamber of the cassette and the second chamber of the cassette.

5. The system of claim **2** wherein each instrument in the plurality of instruments comprises a reagent release system comprising a plurality of protrusions and a second actuator assembly.

6. The system of claim **5** wherein each cassette comprises a first reagent chamber and a second reagent chamber, and wherein the second actuator assembly is configured to move the plurality of protrusions between a first protrusion position, in which each protrusion from the plurality of protrusions is substantially aligned with the first reagent chamber from the corresponding cassette and a second protrusion position, in which each protrusion from the plurality of protrusions is substantially aligned with the second reagent chamber from the corresponding cassette.

7. The system of claim **6** wherein the second actuator assembly is configured to move a protrusion from the plurality of protrusions into contact with a plunger associated with the first chamber of the corresponding cassette to transfer a first reagent from the first reagent chamber into the first chamber, the second actuator assembly configured to move the protrusion from the plurality of protrusions into contact with a plunger associated with the second reagent chamber of the corresponding cassette to transfer a second reagent from the second reagent chamber into the first chamber.

8. The system of claim **7** wherein the second actuator assembly is configured to move the plurality of protrusions along a first axis between the first protrusion position and the second protrusion position, the second actuator assembly is further configured to move the protrusion from the plurality of protrusions along a second axis into contact with the plunger associated with the first reagent chamber.

9. The system of claim **7** wherein the second actuator assembly is configured to move at least a portion of the protrusion from the plurality of protrusions into the first reagent chamber to transfer the first reagent from the first reagent chamber into the first chamber.

10. The system of claim **7** wherein each cassette from the plurality of cassettes includes a puncturable member disposed between the first chamber and the first reagent chamber; and the second actuator assembly is configured to move the protrusion from the plurality of protrusions such that the plunger associated with the first reagent chamber punctures a portion of the puncturable member.

11. The system of claim **7** wherein each cassette from the plurality of cassettes includes a pump configured to mix at least one of the first reagent or the second reagent with the particle within the first chamber; and the second actuator assembly is configured to actuate each pump from the plurality of cassettes.

12. The system of claim **1** wherein the communication device comprises a universal asynchronous receiver transmitter (UART).

13. The system of claim **12** wherein the communication device comprises a universal serial bus (USB).

14. The system of claim **13** wherein the communication device comprises a controller area network bus (CANBUS).

15. The system of claim **1** wherein the network is a wireless network.

16. The system of claim **1** wherein the network is a wide area network (WAN).

17. The system of claim 1 wherein the network is a control area network (CAN).

18. The system of claim 1 wherein the network is a token ring.

19. The system of claim 1 wherein the network is coupled to the internet.

20. The system of claim 1 wherein the network is an Ethernet network.

\* \* \* \* \*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 9,434,939 B2  
APPLICATION NO. : 15/006494  
DATED : September 6, 2016  
INVENTOR(S) : Steve Jia Chang Yu et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

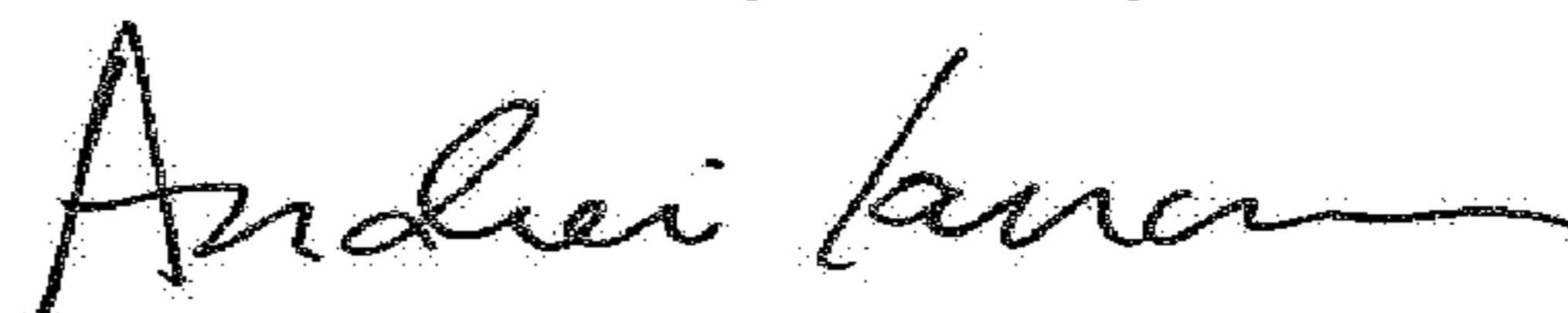
Item (56) References Cited - Other Publications, delete the 2nd reference on page 4 "Office Action, issued in Chinese Application No. 2(11310061818.X, dated Nov. 23, 2015 (English Translation)." and replace with --Office Action, issued in Chinese Application No. 201310061818.X, dated Nov. 23, 2015 (English Translation).-- therefor.

Item (56) References Cited - Other Publications, delete the 9th reference on page 4 "Office Action, issued in Mexican Application No. MX/a/2008/00511, dated Sep. 7, 2010 (English Translation)." and replace with --Office Action, issued in Mexican Application No. MX/a/2008/005115, dated Sep. 7, 2010 (English Translation).-- therefor.

Item (56) References Cited - Other Publications, delete the 24th reference on page 4 "Office Action, issued in Chinese Application No. 21180018623.6, dated Jul. 15, 2014." and replace with --Office Action, issued in Chinese Application No. 201180018623.6, dated Jul. 15, 2014.-- therefor.

Item (56) References Cited - Other Publications, delete the 37th reference on page 4 "Pilosof and Nieman, "Microporous membrane flow cell with nonitnmobilized enzyme for chemiluminescent determination of glucose," *Anal. Chem.*, 54:1698-1701, 1982." and replace with --Pilosof and Nieman, "Microporous membrane flow cell with nonimmobilized enzyme for chemiluminescent determination of glucose," *Anal. Chem.*, 54:1698-1701, 1982.-- therefor.

Signed and Sealed this  
Fifteenth Day of May, 2018



Andrei Iancu  
Director of the United States Patent and Trademark Office